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PONTILE GLIOMAS

A PATHOLOGIC STUDY AND CLASSIFICATION OF TWENTY-FIVE CASES *

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Gliomas of the pons alone or involving together the pons, the adjacent hemisphere of the cerebellum and the cerebellopontile angle are uncommon, if one may judge both from the few cases included in the statistics from neurosurgical clinics and from the individual reports in the literature.

In the collection of 1,737 intracranial tumors verified to July 28, 1929, in the Peter Bent Brigham Hospital, 732 were gliomas. Of the latter, 188 were located beneath the tentorium, in the cerebellum and pons, and 25 were classed as "gliomas of the pons, verified, but unclassified."

The number of verified gliomas of the pons does not give the true incidence of these tumors, because patients for whom the diagnosis of glioma of the pons is unquestioned are rarely operated on, and the opportunity of determining the nature of the lesion may not occur. There are twenty-eight such cases grouped as unverified cases of pontile tumor among 782 unverified cases of intracranial tumor.

The problem of classifying these tumors as the gliomas elsewhere in the brain were classified in this clinic by Bailey and Cushing [1] presented difficulties, for from the study of the specimens removed at operation a diagnosis other than that of glioma could not be made. However, as the entire tumors were eventually available for study, it was found possible to classify these gliomas and to demonstrate, despite local peculiarities in structure, similarities in the gross and histologic structure of these gliomas to previously classified gliomas found elsewhere in the brain.

It is the plan in this study to present the majority of these cases and to illustrate the gross lesion, especially. Only the unusual microscopic details will be illustrated, for the microscopic structure of similar gliomas has been thoroughly illustrated in previous presentations from this clinic. Each classified group will be compared with certain known features of similarly classified gliomas found elsewhere in the brain, and it will be seen that these so-called pontile gliomas differ but little from the larger groups of gliomas found elsewhere in the brain.

* Submitted for publication, Sept. 30, 1929.

* From the surgical clinic and laboratory of the Peter Bent Brigham Hospital.

1. Bailey, P., and Cushing, H.: A Classification of the Tumors of the Glioma Group, Philadelphia, J. B. Lippincott Company, 1926.

MATERIAL AND METHODS

The entire tumor of each patient was available for study. From the formaldehyde-fixed material, paraffin sections were stained with hematoxylin and eosin and phosphotungstic acid hematoxylin after the method suggested by Davidoff.[2] Frozen sections of the same material were stained with gold chloride sublimate, the Globus[3] modification being used, and for oligodendroglia and microglia by Penfield's[4] combined method.

GLIOBLASTOMA MULTIFORME

One hundred and fifty-two examples of glioblastoma multiforme are included among the 732 gliomas verified in this clinic. These tumors were found to have many features in common in that they were invasive and rapidly growing tumors of the cerebral hemispheres with abundant areas of necrosis, hemorrhage and cyst formation. The great majority occurred in adults of middle age, with but few occurring in young adults. The life history of these tumors was measured in months. The varied histologic character of these tumors has been described by Globus and Strauss,[5] and Cushing and Bailey.[1]

Ten of the twenty-five verified gliomas of the pons were assigned to this group. They were marked by a short duration of life after the onset of symptoms and by a gross and histologic appearance similar in many respects to that of the described previously verified examples of glioblastoma multiforme. There was but one difference in that the age incidence of this small group of cases was the opposite from what was to be expected with present knowledge of the usual age incidence of these gliomas. Whereas these tumors are commonly found in middle-aged patients, seven of the cerebellopontile cases occurred in children and young adults and but three cases occurred in adults, of 23, 37 and 59 years of age, respectively.

The onset of symptoms in these patients was commonly with evidence of involvement of the oculomotor nerves or with signs of increased intracranial pressure. Eventually, in the course of the illness, every patient gave evidence of some involvement of the oculomotor nerves as well as of other cranial nerves, notably, the sensory division of the trigeminal and the peripheral distribution of the facial nerve. Increased intracranial pressure occurred early in eight of the cases.

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2. Davidoff, L. M.: Staining Fibrillary Neuroglia in Formalin Fixed Material, Am. J. Path. **4**:493, 1928.

3. Globus, J. H.: The Cajal and Hortega Glia Staining Methods: A New Step in the Preparation of Formaldehyde Fixed Material, Arch. Neurol. & Psychiat. **18**:263, 1927.

4. Penfield, W.: A Method of Staining Oligodendroglia and Microglia (Combined Method), Am. J. Path. **4**:153, 1928.

5. Globus, J. H., and Strauss, I.: Spongioblastoma Multiforme, Arch. Neurol. & Psychiat. **14**:139, 1925.

The interval from the onset of symptoms to the fatal termination was short, averaging but four months. The shortest survival period was one month and the longest seven months. A lesion of the brain stem or of the cerebellum was suspected in each patient because of the multiple cranial nerve paralysis, increased intracranial pressure and involvement of the sensory and motor pathways. Seven of the patients appeared to have such an extensive and inaccessible lesion that an operative procedure was not considered. Suboccipital explorations were made in the remaining four patients in the hope that a tumor of the cerebellum or of the lateral recess would be encountered which could be attacked surgically. However, an early postoperative fatality resulted in each instance.

A postmortem examination of the brain of each patient was made. This gave the unusual opportunity of correlating the clinical symptoms with the lesion and also allowed the assembling of such material that comparison with the gross number of known classified tumors was possible.

The examination of the external aspect of the brain stem showed that in nine of the ten specimens the tumor involved one side of the pons alone or more of one side than of the other side. From one side, the tumor projected into the angle between the pons and the cerebellum to merge with the cerebellum. This part of the tumor never appeared to be enucleable. In two specimens, in addition to the lateral extension, there was a projection of the tumor forward to the interpeduncular space and posteriorward to underly the medulla. In every case, the inferior aspect of the pons had a corrugated appearance owing to the fact that the basilar artery and its branches became partially or completely buried in the expanding tumor and thus formed a series of ridges of tumor. Occasionally, one of the cranial nerves, usually the sixth, was strangulated by one of the cerebellar branches of the basilar artery on the side opposite the tumor. In every instance there was involvement of some of the cranial nerves by the tumor; the second, fifth, sixth, seventh and eighth nerves often were surrounded by the tumor or were stretched over the projecting growth. These nerves or their nuclei were either involved by the tumor or strangulated by branches of the basilar artery. This was particularly true of the abducentes nerve. In two cases there was evidence in the gross of the tumor's invading the subarachnoid spaces and growing out along the trigeminal nerve to the gasserian ganglion.

Some of the brains were cut in the sagittal, and others in the coronal, plane. It was impossible to make out the point of origin of any of these tumors because of the necrosis, hemorrhage, cyst formation and size of the lesion. However, in eight instances the tumor involved one or both sides of the pars basilis, and in two it involved only one side

of the pars dorsalis. In every case, it involved the brachium pontis and one of the hemispheres of the cerebellum. The crus cerebri was extensively invaded along with the pons, in one case, and the medulla oblongata was invaded in four instances. Given a coronal section through a tumor replacing a part of the pons, the brachium pontis and the cerebellar hemisphere on the same side, one would find it difficult to say just where the lesion began.

In every instance, the tumor was soft and contained multiple areas of necrosis, small and large hemorrhages and cysts, as well as scattered translucent areas of cellular appearing tissue. The color of the cut surface varied with the necrosis, cyst contents and age of the hemorrhages. In several cases in which the tumor was examined but a few months after the onset of the symptoms, there were apparent lines of demarcation between the tumor and the pontile nerve tracts. However, on microscopic examination, there appeared to be no line of demarcation. There were varying degrees of dilatation of the third and lateral ventricles, as the fourth ventricle was frequently almost completely occluded by the projection of a cystic part of the tumor or of the entire tumor into this space.

As the clinical histories and gross specimens of these cases compared favorably with those of known verified cases of glioblastoma multiforme, so did the histologic appearances. The local peculiarities of structure, especially the crossing of the fiber tracts, made the general arrangement of the tumor of the pons differ from that of the tumor of the cerebrum. Areas of degeneration, hemorrhages, old and recent, and cyst formations were found everywhere. The cells varied in size, shape and preservation. The most common cells were those with oval-shaped bodies and with or without processes. Larger, rounded cells and multinucleated cells, with their nuclei variously arranged, were abundant. Astrocytes were less common, and in no case were there seen fields in which the cells appeared to be differentiating into astrocytes. In the pons, the pattern of growth differed at the periphery, because the cells invaded along the course of the nerve fiber tracts (fig. 12). This gave a checkered appearance to the better preserved areas. Elsewhere, the necrosis determined the arrangement of the cells. The changes in the blood vessels varied. In the early cases there was but little change, while in the instances in which the period of survival was the longest there were just such changes as are described by Globus and Strauss [5] and Bailey and Cushing; [1] namely, irregular proliferation of the adventitia and occlusion of the lumen by proliferation of cells beneath the endothelial lining.

Any of the ten cases in this group could be considered as material for a single case report because of its many interesting clinical and pathologic features. However, seven of the cases are described, each to illustrate either some special clinical or a pathologic observation.

Microscopic descriptions of the individual tumors are not included, as this part of the study is considered in the introduction.

The first two cases are examples of glioblastoma of the pons with a short history, two months in all. One case was mistaken for a tumor of the cerebellum and the other for an encephalitis.

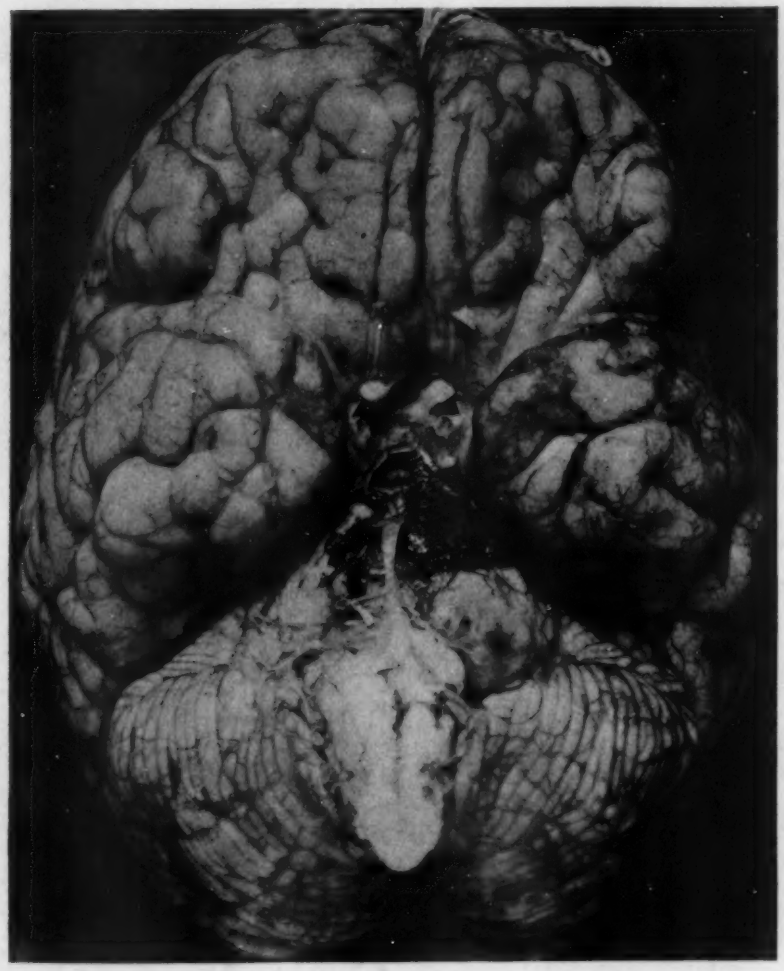

Fig. 1 (case 1).—Glioblastoma multiforme involving the left side of the pons and extending out into the left cerebellopontile angle. A recent hemorrhage has broken through the tumor into the subarachnoid space.

CASE 1.—*Rapid onset with paralysis of left sixth and seventh nerves. General pressure symptoms. Pseudocerebellar signs and symptoms. Suboccipital exploration yielding no definite evidence of a tumor. Death. Necropsy disclosed tumor of pons.*

History.—On Sept. 18, 1928, Mary O'B., aged 6, was referred for observation. The child was normal until seven weeks before admission, when a sudden paralysis of the left sixth and seventh cranial nerves developed. One week later, a staggering gait was noticed. Within five weeks after the onset, signs and symptoms of increased intracranial pressure developed, so that immediate hospitalization was warranted.

Physical Examination.—The child was mentally alert. There was paralysis of the left sixth and seventh nerves and involvement of the sensory part of the left fifth nerve. A coarse lateral nystagmus was present. The gait was of the cerebellar type. The deep reflexes were exaggerated. The cutaneous sensitivity

Fig. 2 (case 1).—A sagittal section through the tumor seen in figure 1 shows a moderate dilatation of the third ventricle and partial occlusion of the fourth ventricle. The hemorrhages in the tumor are extensive.

over the entire left side was lessened. The optic disks showed a choking of 4 diopters. There were marked hypotonia and ataxia of the extremities.

Course of Illness.—A preoperative diagnosis of cerebellar tumor was made. A suboccipital exploration disclosed evidence of increased pressure, but no tumor. Death occurred two days after operation.

Necropsy.—A large, soft mass replaced the basilar and part of the dorsalis region of the left side of the pons and extended both into the left cerebellopontile angle, into the right side of the pons and up and under the left cerebellar hemisphere. A recent hemorrhage extended from the middle of the tumor out into

the subarachnoid spaces over the anterior portion of the pons. The tumor was huge, soft, with two large and many small hemorrhages. It presented only occasional small cysts. There was a moderate dilatation of the third and lateral ventricles. The aqueduct of Sylvius was not dilated. The left sixth and seventh nerves were imbedded in the tumor (figs. 1 and 2).

Comment.—The rapid development of the disease with early symptoms of general intracranial pressure suggested the presence of a tumor in the posterior fossa, probably in the cerebellar hemisphere. How-

Fig. 3 (case 2).—The irregular appearance of the base of the pons is caused by the indentation of a soft glioblastoma multiforme by surface blood vessels. The third and fifth nerves are surrounded by the tumor. The left sixth nerve is strangulated by the anterior inferior branch of the cerebellar artery.

ever, the early involvement of the left sixth and seventh cranial nerves and the sensory tracts on the left side was against the lesion's being in the cerebellum, for such lesions are only occasionally seen in tumors of the cerebellum. The rapid progress of the disease and the immediate cause of death were undoubtedly due to the extensive hemorrhages.

CASE 2.—*Onset with weakness of left hand. Paralysis of left facial nerve. Vomiting. Dysarthria. Dysphagia. Spastic paralysis of left side. Lateral nystagmus. Subtemporal decompression. Quadriplegia. Death occurred three weeks after operation. Necropsy disclosed tumor of pons.*

Clinical History.—On June 29, 1927, Jean S., a 6 year old school girl, was referred with a diagnosis of cerebellopontile tumor. Three weeks before her admission, definite weakness of the left hand was observed. One week later, left facial paralysis and weakness of the left lower leg developed. More acute symptoms began six days before her admission, with dysarthria, dysphagia and paralysis of the right third nerve.

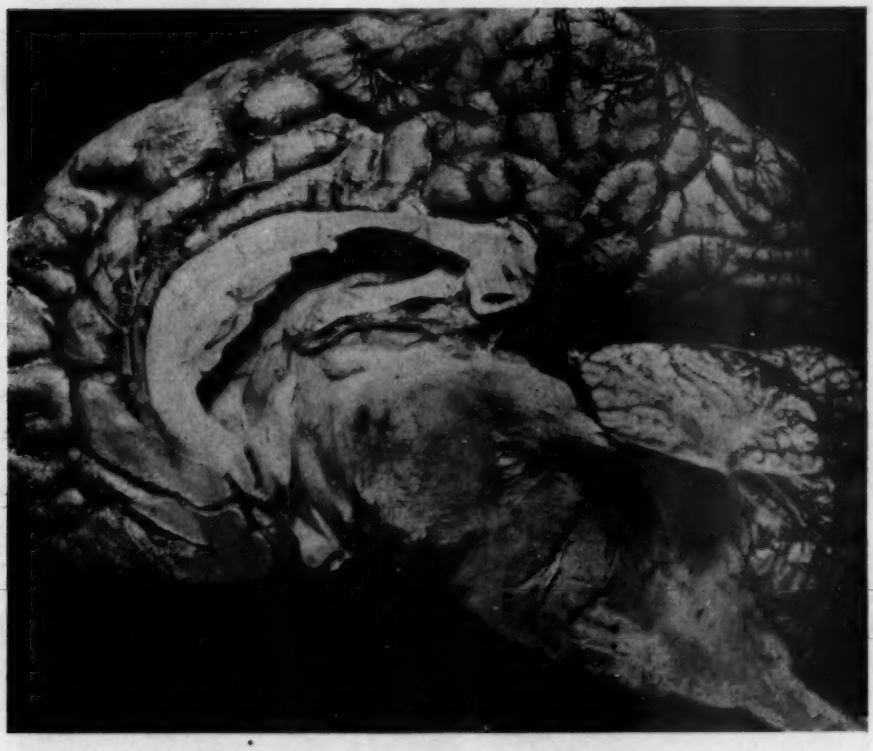

Fig. 4 (case 2).—This sagittal seciton of the tumor seen in figure 3 shows the involvement of the pons, medulla and crus cerebri. The fourth ventricle is almost obliterated.

Physical Examination.—There was spastic hemiplegia of the left side and paralysis of the left facial nerve and the right third nerve. The right pupil was smaller than the left. There was persistent, slow nystagmus of the left eye upward and to both sides. There was a positive Babinski reflex and ankle clonus on the left side. The optic disks appeared normal.

Course of Illness.—The great variation in the clinical symptoms suggested to the observers epidemic encephalitis with special involvement in the pons and right crus cerebri. The nasal margins of the optic disks showed beginning swelling soon after admission. Soon there developed complete quadriplegia, evi-

dence of paralysis of other cranial nerves and severe acidosis. Death occurred on July 27, 1927, about seven weeks after the onset of the first symptoms. A complete necropsy was performed.

Necropsy.—The pons was irregularly enlarged by multiple, soft nodules, varying in size, which spread in the subarachnoid spaces as far forward as the point of emergence of the third nerves (fig. 3). The growth extended far into the interpeduncular space, indenting the left uncinate region, to involve the right crus cerebri. The basilar artery was almost completely imbedded in the tumor. The sagittal section showed the enormous size of the tumor, which compressed but did not fill the third ventricle (fig. 4). It involved almost the entire pons and right crus cerebri and invaded the fourth ventricle. The tissue was soft, necrotic, with multiple small hemorrhages and two large fresh hemorrhages.

Comment.—On admission, the main physical observation was that of Weber's syndrome with complete paralysis of the oculomotor nerve and complete paralysis of the left side. The extensive involvement of the pons and the right crus cerebri could well explain the Weber's syndrome, as the oculomotor nerve went through the growth. With the development of the swelling of the optic disks, a diagnosis of tumor of the pons with extension to the right crus cerebri was made, and an operative procedure was not considered advisable.

The next case represents another of the difficulties in the diagnosis of the subtentorial tumors.

CASE 3.—*Onset with staggering gait and bilateral ptosis. Dysarthria, dysphagia and rapid development of increased intracranial pressure. Suboccipital exploration for presumed midline cerebellar tumor with early fatal results. Necropsy disclosed tumor of pons and cerebellum.*

Clinical History.—Bertha P., aged 4, was referred on July 26, 1928, for observation. About four months before the patient's admission, her mother noticed that she staggered and often fell to the right side. At the same time ptosis of both eyelids developed. Dysarthria, dysphagia and the signs and symptoms of increasing intracranial pressure were evident in the month before admission.

Physical Examination.—The patient was stuporous. Hypotonicity of all the muscles of the body was noted. The optic disks were swollen to about 5 diopters. Bilateral paralysis of the third nerves and loss of both corneal reflexes were evident. All superficial and deep reflexes were absent.

Course of Illness.—It was difficult both to get an accurate history and to make a complete examination of this patient. In the belief that the lesion might be a midline medulloblastoma of the cerebellum, a suboccipital exploration was made on July 30, 1926. The midline and fourth ventricle appeared to be filled with tumor. A piece of the bulging floor of the ventricle was taken for histologic section. The child was in poor condition, even before the operation, and died two days afterward. Necropsy was performed.

Necropsy.—At the first examination of this brain, the pons was described as a huge, firm mass with the left side appearing smaller than the right side. A mesial section showed the diffuse, symmetrical enlargement projecting into the fourth ventricle. After a second examination, the extension of the tumor into the right cerebellopontile angle and the cerebellum was seen (fig. 5). This part

of the tumor was soft and necrotic and closely resembled other examples of glioblastoma multiforme. The many nodular projections over the base represented tumor masses growing up between the constricting transverse blood vessels.

Comment.—A preoperative diagnosis of midline tumor of the cerebellum, probably medulloblastoma, was made. The absence of nystagmus, the presence of hypotonicity, the increased intracranial pressure and the staggering gait suggested a lesion of the cerebellum located in the midline. This is the youngest patient with glioblastoma multiforme encountered in this clinic.

Fig. 5 (case 3).—The basilar surface of this glioblastoma of the pons and adjacent parts is like that seen in case 2. The basilar artery and its branches run in grooves through the tumor. This large, soft tumor extended into both cerebellopontile angles.

Six of the patients with pontile glioblastoma multiforme first complained of staggering gait and falling to one side. In each of these cases, it is most interesting to note that the tumor involved one hemisphere of the cerebellum and the brachium pontis and but a small portion of the pons. In each of these cases, the adjacent cerebellopontile angle was involved.

CASE 4.—*Onset with paralysis of right fifth and third nerves. Early symptoms of general intracranial pressure. Deafness (right ear). Paralysis of right facial nerve. Left hemiplegia and hemihypesthesia. Suboccipital exploration. Death. Necropsy disclosed tumor of the pons and cerebellum.*

History.—On Jan. 4, 1910, Madeline H., aged 15, was admitted to the Johns Hopkins Hospital as a brain tumor suspect. The patient was normal until five months before admission, when the present illness began with numbness in the right side of the face and drooping of the right eyelid. In rapid succession appeared symptoms of general pressure, ataxia, severe occipital headaches, pain on flexion of the head and left hemiplegia.

Physical Examination.—The patient was dull and complained of a stiff neck. The pupils were unequal and nystagmus in all directions was present. Both optic disks were swollen to about 5 diopters. There was an incomplete paralysis of the right abducens and facial nerves. Hypesthesia over the right trigeminal

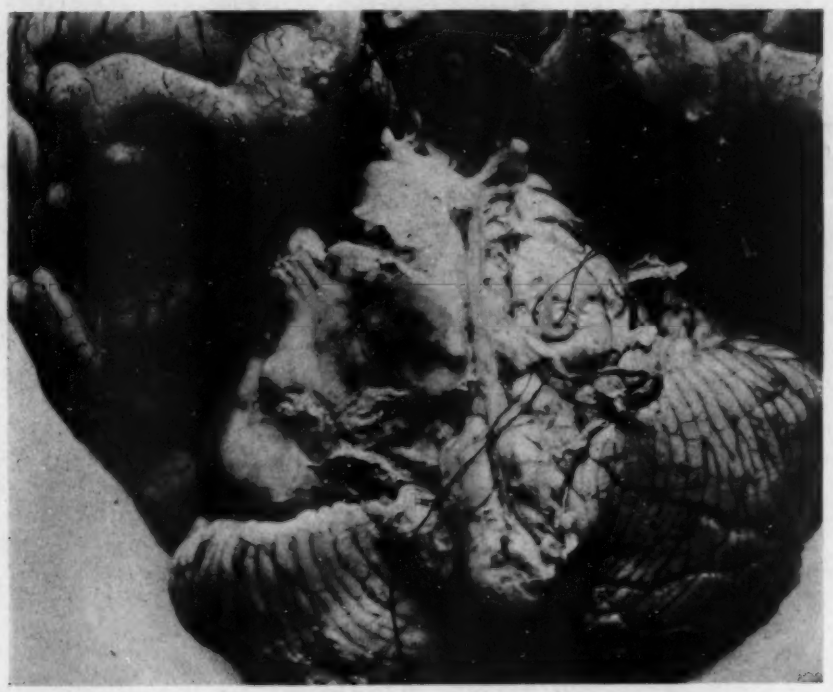

Fig. 6 (case 4).—This glioblastoma involved the right side of the pons, grew out into the angle and completely surrounded the right third and fifth nerves. The threads pull apart the left sixth nerve from a branch of the cerebellar artery which had strangulated the nerve.

field and the left side of the body was present. A coarse ataxia and adiadokokinesis were noted.

Course in the Hospital.—On Jan. 6, 1910, a suboccipital exploration was made, with negative results, and early postoperative death occurred. An examination of the head was made.

Necropsy.—The entire right half of the pons was replaced by a large, soft tumor which extended down and back to the level of the olivary body. This tumor filled the entire right cerebellopontile angle and compressed the right cerebellar

hemisphere. On the right side, the cranial nerves from the third to the eighth inclusive were involved by the tumor. On the left side, the sixth nerve only was involved, and this was compressed and flattened by the overlying branch of the left posterior cerebellar artery.

Coronal sections showed a dilatation of the third and lateral ventricles, with the fourth ventricle compressed and flattened by the tumor. The tumor extended into the left side of the pons and also through the right brachium pontis to the right hemisphere of the cerebellum.

The extensive involvement of the entire right side of the pons is shown in figure 6. The cut surface is typical of that of glioblastoma multiforme (fig. 7). The multiple cysts, hemorrhages and large areas of necrosis made up the greater portion of the tumor. The subarachnoid space about the tumor was invaded, and the tumor cells surrounded the entire sensory root of the right fifth nerve even out to the gasserian ganglion.

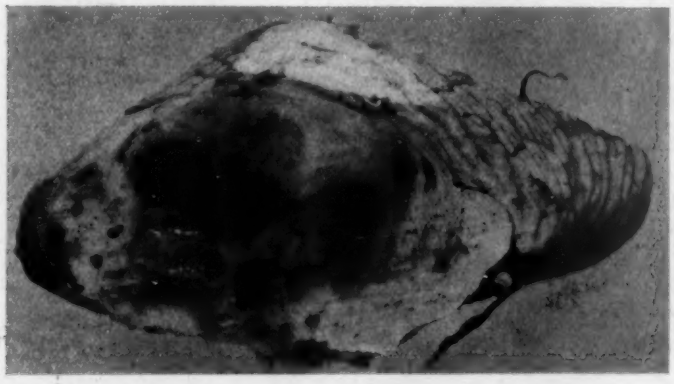

Fig. 7 (case 4).—This represents a coronal section through the pons, the cerebellopontile angle and the right cerebellar hemisphere of the brain seen in figure 6. The hemorrhage, necrosis and multiple cysts are typical of this type of glioma.

Comment.—From the clinical and pathologic standpoints, this is an excellent example of glioblastoma multiforme of the pons. The preoperative period of illness was short, and there was evidence of extensive involvement of the cranial nerves on the right side and left hemiplegia and hemihypesthesia. The large soft, infiltrating, degenerated and degenerating tumor with multiple cysts and areas of hemorrhage was typical of other cases in this group.

In his article on strangulation of the nervi abducentes by lateral branches of the basilar artery, Dr. Cushing [6] included this case as one of the illustrations of the sixth nerve being involved by the stretched artery on the side opposite to the tumor. In this article, attention was

6. Cushing, H.: Strangulation of the Nervi Abducentes by Lateral Branches of the Basilar Artery in Cases of Brain Tumor, Brain **33**:204, 1910-1911.

also called to the fact that the transverse arteries may cut so deeply into the tissues as actually to lie below the level of the surface. This feature of the tumors is well illustrated in figures 3, 5, 8 and 9.

As in cases 1 and 3, the tumor involved one side of the pons more than the other. The two patients lived for four months and had symptoms of general pressure.

The gross specimen showed the thickened right fifth nerve surrounded by the tumor. The eighth nerve was not found.

CASE 5.—*Onset with attacks of right internal squint, headache and spasm of muscles of left side of neck. Weakness of left side. Staggering gait. Dysarthria. Diplopia. Symptoms of general pressure. Diagnosis of tumor of pons. No operation. Death. Necropsy.*

Clinical History.—On Feb. 16, 1923, Mary F., aged 13, was referred for observation. The symptoms of the present illness began six and a half months before admission, with transient attacks of right internal squint, slight headache and spasm of the left sternomastoid and trapezius muscles. Six weeks later, definite weakness of the left leg and hand were noted. Meanwhile, the attacks of torticollis and internal squint became frequent and severe. The patient became drowsy and weak and had a staggering gait, diplopia and dysarthria, so that she was hospitalized elsewhere from Oct. 2, 1922, to Dec. 11, 1922. After discharge, she went to school until Jan. 9, 1923; then persistent vomiting began and lasted for three days. During the next month, incontinence of urine, inability to swallow and left hemiplegia developed.

Physical Examination.—The patient was comatose, and complete left hemiplegia was present. There was bilateral involvement of the fifth, sixth and seventh nerves. The optic disks showed a high grade of choking, with secondary atrophy.

Course of Illness.—A diagnosis of glioma of the pons was made. Death occurred three days after admission. Necropsy was allowed.

Necropsy.—The entire brain stem was distorted by a large, diffuse, soft tumor which spread out into both recesses and extended as far forward as the interpeduncular space (fig. 8). The tumor involved the right side of the pons and medulla more than the left side. The basilar artery was imbedded in the tumor and ran a tortuous course through it. The branches of this artery disappeared in the tumor. The fifth, sixth, seventh and eighth cranial nerves on either side were difficult to distinguish, as they were imbedded in the tumor. The sections through the pons and medulla showed that the entire right side of the pons and the entire dorsal part of the left side of the pons were replaced by a soft, varicolored tumor with multiple cysts and hemorrhages. The tumor involved the medulla and the cerebellum on the right side and jutted up into the fourth ventricle. From many sections it appeared that the dorsal part of the pons was first involved.

Comment.—This patient had been in four separate hospitals and was considered as having encephalitis and chronic meningitis. On admission to this hospital, the patient presented the clinical picture of tumor involving the pons and the cerebellum.

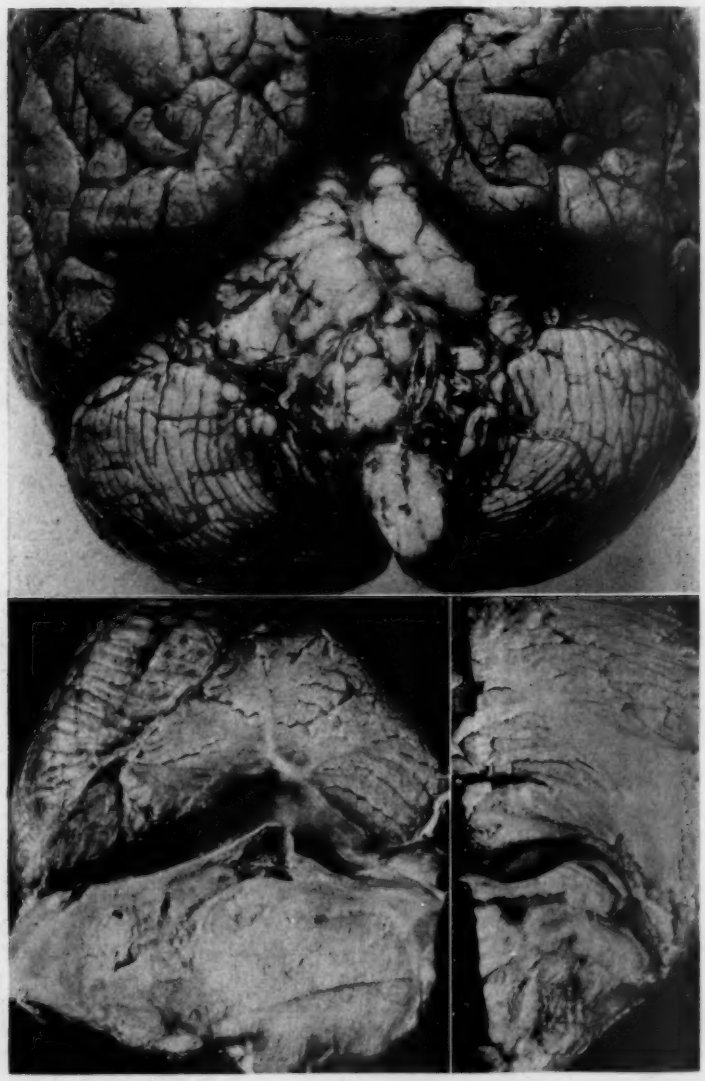

Fig. 8 (case 5).—This glioblastoma involves the base of the pons as do the tumors seen in cases 2 and 3. The blood vessels are buried, and the cranial nerves are difficult to locate. The sagittal and coronal sections show a soft, necrotic and cystic tumor surface.

CASE 6.—*Bilateral paralysis of the sixth, seventh, ninth, tenth and twelfth nerves. Quadriplegia. Diagnosis of tumor of pons. Roentgen therapy with temporary relief. Death. Necropsy.*

Clinical History.—On May 2, 1928, Greta L., aged 13, was referred with a diagnosis of tumor of the brain. About ten weeks before the child's admission, the mother noticed that the child held her head retracted toward the right. One week later, a left internal strabismus developed suddenly. Despite this, the patient

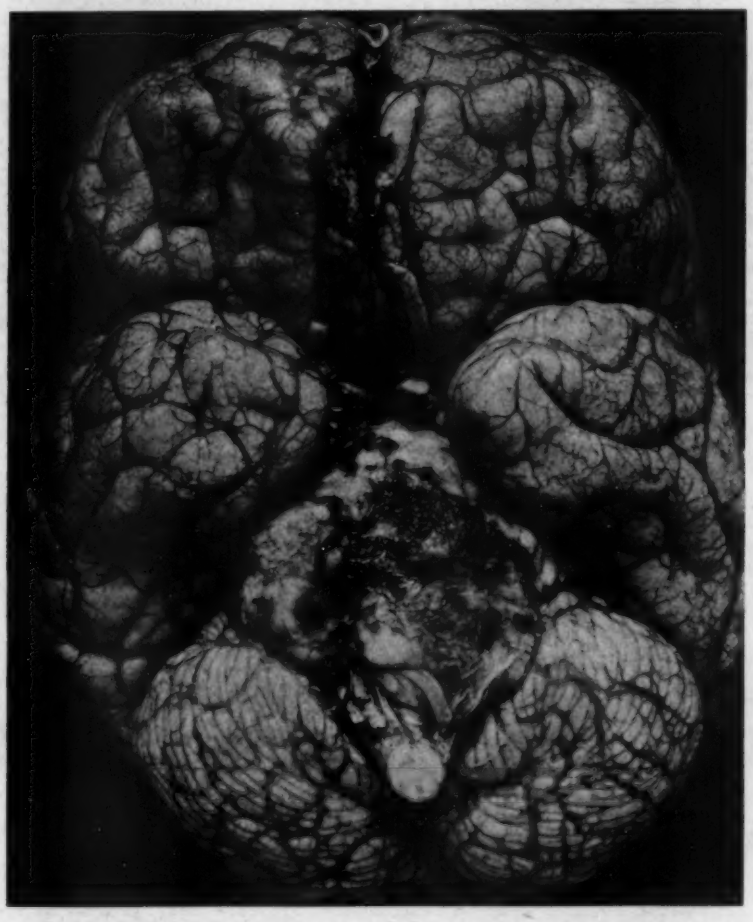

Fig. 9 (case 6).—This large glioblastoma has completely overgrown cranial nerves and blood vessels.

continued at school for two weeks, until the sudden onset of a progressive paralysis of the right leg and arm, both sides of the face and tongue. She complained of an occasional occipital headache. There were no symptoms of increased intracranial pressure.

Physical Examination.—The child was mentally alert. Right hemiplegia with contracture and paralysis of the left upper extremity was associated with bilat-

eral paralysis of the sixth, seventh, ninth, tenth and twelfth cranial nerves. There was no sensory disturbance. A slight choking of the optic disks was seen.

Course of Illness.—A diagnosis of tumor of the pons was made. Several courses of roentgen therapy were given, with temporary relief. Death occurred seven months from the onset of the symptoms. Necropsy was performed.

Necropsy.—The entire basilar surface of the pons was covered by a soft, often necrotic, cystic mass which extended into the cerebellopontile angles, forward to the infundibulum and backward to overlap the medulla (fig. 9). The basilar artery disappeared into the growth. Many other arteries from the anterior part of the medulla bridged over the space between the tumor and the medulla and disap-

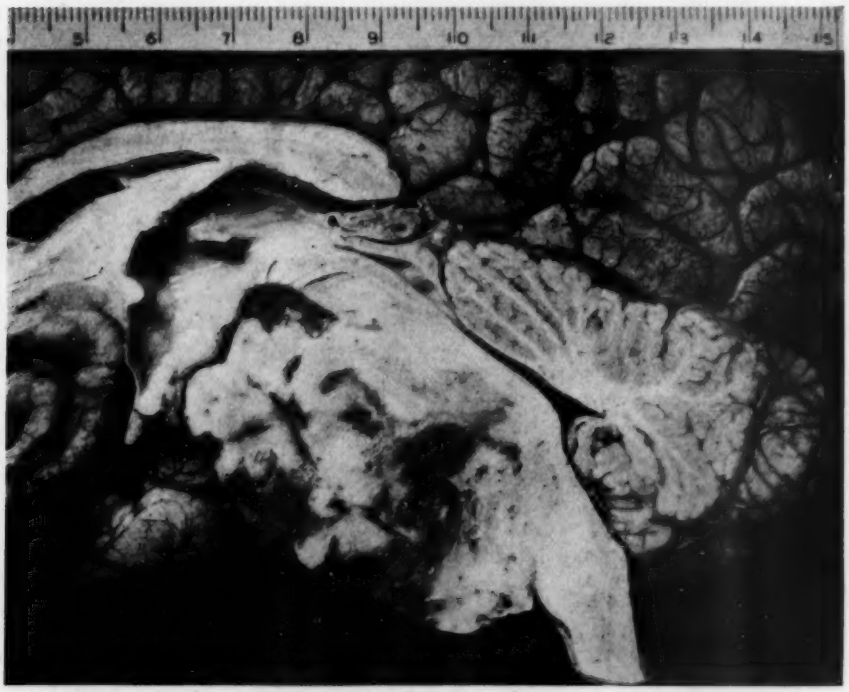

Fig. 10 (case 6).—This sagittal section of the tumor seen in figure 9 shows the typical cut surface of the glioblastoma. The fourth ventricle is compressed, and the third and lateral ventricles are dilated.

peared into the tumor. This growth did not adhere to the adjacent cerebellum. By pushing it aside, the fifth and eighth nerves on either side were seen to be uninvolved by the tumor. The third and ninth nerves appeared to be compressed. The other cranial nerves were not recognized. The surface exposed by the sagittal section was an excellent illustration of a glioblastoma multiforme arising from the anterior and basilar portion of the pons (fig. 10).

Comment.—The diagnosis of extensive glioma of the pons was made because of the involvement of so many of the cranial nerves and of the motor and sensory pathways. The tumor appeared to be the largest

of the series of tumors seen in the region of the pons. The patient was given several courses of roentgen ray treatments and appeared to improve temporarily after each one.

CASE 7.—*Onset with tinnitus (left), present for four years. Recently, staggering gait. Occipital headaches (left). Nausea, vomiting. Complete deafness, one month. Various hospitalizations. Ataxia. Hyperesthesia, left side of face. Diagnosis of probable left acoustic neurinoma. Suboccipital exploration with finding of tumor of pons filling left lateral recess. Death twelve days after operation. Necropsy disclosed tumor of cerebellum and pons.*

Clinical History.—On April 1, 1929, Pauline W., aged 37, was referred with a diagnosis of tumor of the left cerebellopontile angle. For four years before

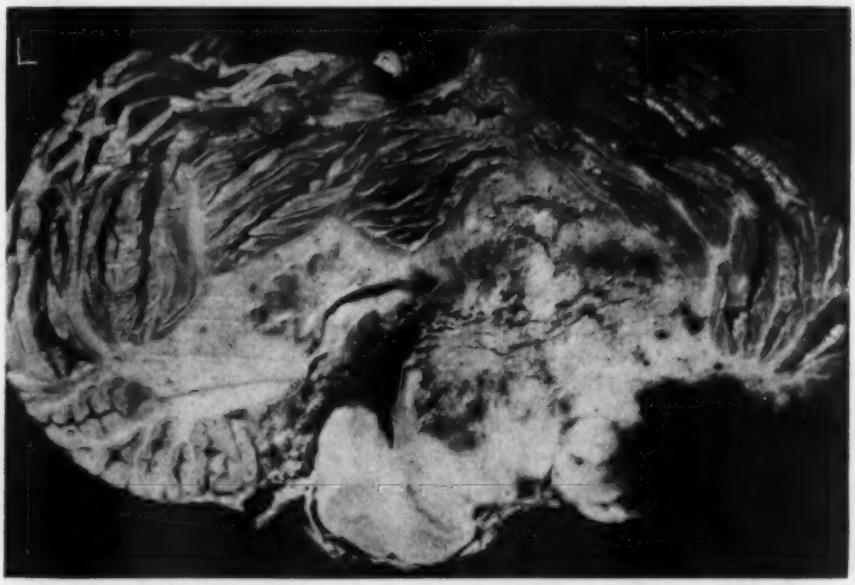

Fig. 11 (case 7).—A part of this large glioblastoma was removed from the right cerebellar hemisphere at operation. The brachium pontis and the dorsal portion of the right side of the pons are involved.

admission, the patient had tinnitus in the left ear but no deafness. She was well until four months before admission, when staggering gait, increase in severity of a left occipital headache and dizziness forced her to go to bed. Complete deafness in the left ear and tinnitus in the right ear with persistent nausea and vomiting were present for the month before admission.

Physical Examination.—The patient was drowsy and emaciated. Nystagmus in all directions was present. There was hyperesthesia over the left side of the face, ataxia of the extremities, especially of the left side, and suboccipital tenderness. There was complete deafness in the left ear. The optic fundi showed engorgement of the veins.

Course of Illness.—The patient was emaciated, dehydrated and in poor condition. However, a suboccipital exploration was begun. As no evidence of a

hydrocephalus was found on tapping the ventricles, the operation was stopped. Ventriculograms were unsuccessful. On the following day, the suboccipital exploration was made, and a glioma of the left side of the pons was demonstrated. A postoperative infection with *Staphylococcus albus* occurred, and death resulted twelve days later. Necropsy was performed.

Necropsy.—An infected thrombus was found in the left lateral cerebral sinus. There was a localized meningitis which obscured the structures over the base of the brain.

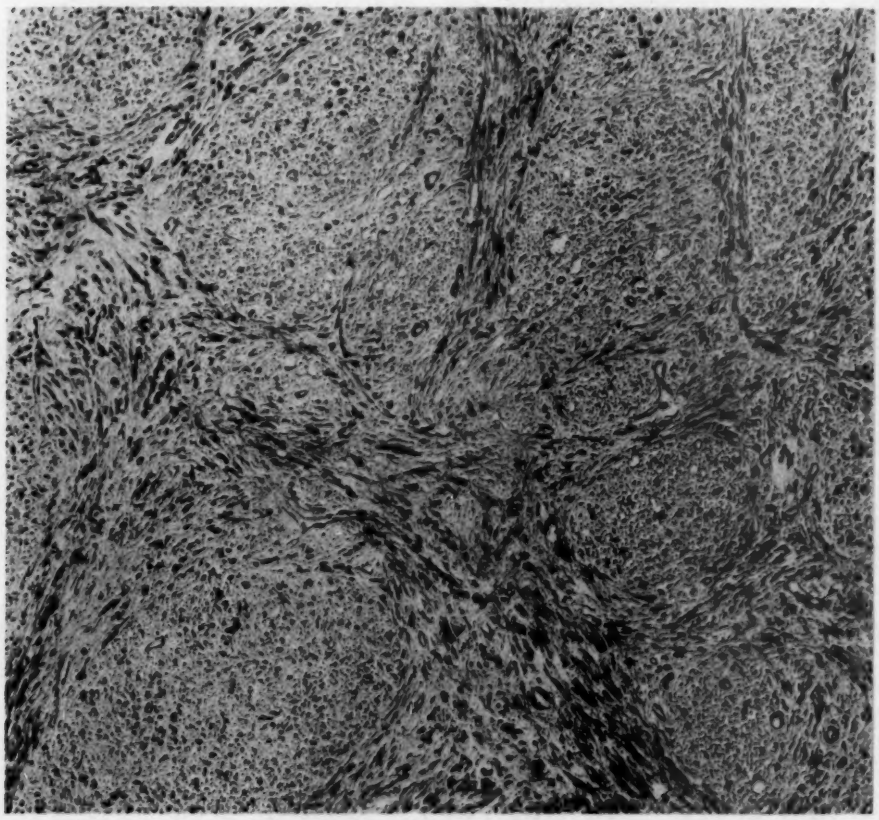

Fig. 12 (case 7).—This photomicrograph represents the usual picture at the periphery of the glioblastoma; × 100. It shows the cells invading between the fiber tracts. Phosphotungstic acid hematoxylin used.

The results of the recent operation were shown on the uncapping of the left hemisphere of the cerebellum and a portion of the tumor. There was no distortion of the medulla, pars basalis of the pons or the large basilar arteries. The cranial nerves on the left side appeared normal. On the right side, the eighth cranial nerve was not seen. The right fifth nerve was surrounded by tumor.

The coronal sections showed a soft, partially necrotic, gray-white tumor infiltrating the left pars dorsalis of the pons, the left brachium pontis, the left cerebellar hemisphere and the left side of the dorsum of the medulla oblongata

(fig. 11). The tumor also extended up into the fourth ventricle and partially occluded it. At one point it was adherent to the ependymal lining on the opposite side of the ventricle.

Comment.—It is impossible to evaluate the history of tinnitus for four years before the onset of the acute intracranial symptoms. It may be possible that a glioblastoma can be present over a long period of years and then begin to grow rapidly.

The onset with staggering gait, dizziness and headache suggested a tumor of one cerebellar hemisphere. The fact that deafness occurred late in the course and that there were no evidences of papilledema was not in favor of a primary acoustic tumor.

The gross specimen suggests that in this case the growth began in the cerebellar hemisphere and then involved the dorsalis pontis, a part of the pons which has not been commonly found involved by glioma.

SPONGIOBLASTOMA UNIPOLARE

Twenty-four examples of spongioblastoma unipolare appear among the gliomas verified in this clinic. Seven of these tumors were located in the cerebrum and eight in the cerebellum and nine were recently classified from among a group of sixteen verified but previously unclassified gliomas involving the optic chiasm and optic nerves.

Fifteen of the seventeen examples of spongioblastoma unipolare found in the chiasm and in the cerebellum occurred in children under 15 years of age. Six of the seven patients with this type of glioma in the cerebrum were adults.

These tumors are usually slow growing; for this group the average period of survival after the onset of symptoms was over four years. However, the course of illness in five of the eight children with spongioblastoma unipolare in a cerebellar hemisphere was much shorter.

It is of interest that the ages of the five patients herein included were 13, 29, 34, 38 and 59 years, respectively, showing again the contrast in ages seen in comparing the group of patients with glioblastoma multiforme.

There were no special similarities in the clinical histories of the five patients of this group, except that two patients were suspected of having acoustic tumor.

The average duration of life from the onset of symptoms until death was two years, with the extremes being four months and four years. Two of the patients were considered as having pontile tumors and were not operated on, while three patients had suboccipital explorations. Two of these patients died shortly after operation, and one patient lived for one year.

The tumors were firm and gray, with small and large cysts and little gross evidence of necrosis. Usually, one side of the pons was

involved, and the tumor tended to grow out into the adjacent angle and downward to invade or overhang the medulla. Consequently, the cranial nerves, especially the sixth, seventh and eighth, were involved on one side.

Although this type of glioma is classified as unipolar spongioblastoma, the cells of the tumor consist of spongioblasts with either one or two processes, as well as of astrocytes in variable number. The cells are variously arranged, either in parallel groups or about blood vessels or areas of degeneration. The cells of the tumors in this series were

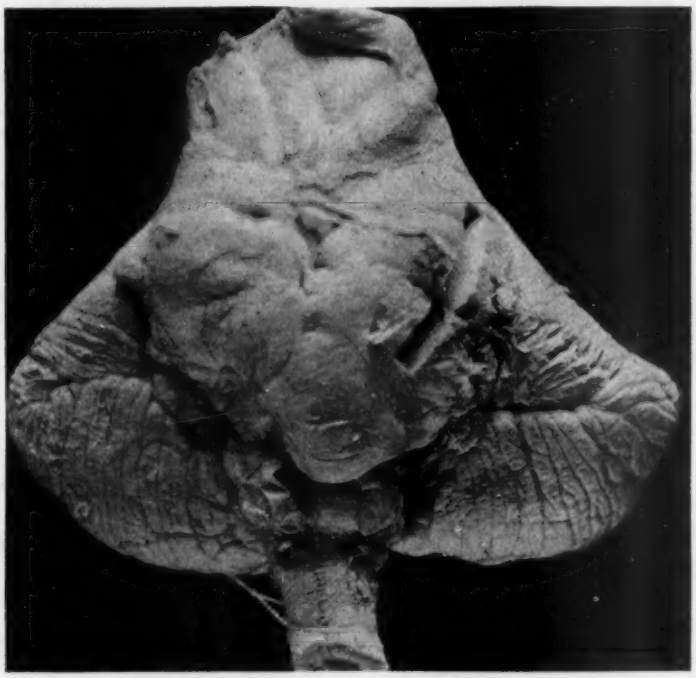

Fig. 13 (case 8).—This large unipolar spongioblastoma has grown over the basilar vessels and the cranial nerves.

frequently arranged parallel and appeared to grow down and along the fiber tracts (fig. 14). Small and large cysts were present, and small areas of necrosis were frequent. The cells were often grouped about the smaller areas of necrosis with their processes extending toward the necrotic area.

The histories of three of the five patients with unipolare spongioblastoma will be presented. The clinical diagnoses of these three cases were glioma of the pons, glioma of the cerebellum and glioma of the cerebellopontile angle, respectively.

CASE 8.—*Onset with emotional disturbances and diplopia. Symptoms of general pressure. Weakness and paralysis of entire right side. Deafness (right). Dizziness. Dysarthria. Subtemporal decompression. Death two months later. Necropsy disclosed tumor of pons.*

Clinical History.—On March 14, 1913, Angelina M., aged 13, was referred with a diagnosis of tumor of the brain. One year before her admission, the onset of the illness began with diplopia and the symptoms of increased intracranial pressure. In the month before admission there was a gradual onset of weakness and paralysis of the right side, deafness of the right ear, dizziness, dysarthria and difficulty in swallowing.

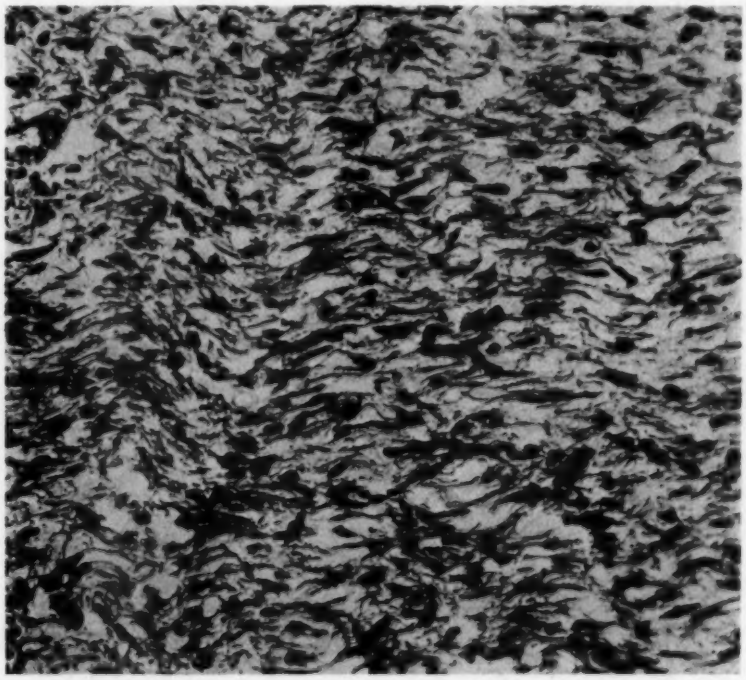

Fig. 14 (case 8).—The cells of this unipolar spongioblastoma tend to arrange themselves uniformly in parallel rows; stained with phosphotungstic acid hematoxylin; × 600.

Physical Examination.—The patient was well nourished. There was paralysis of the left abducens nerve and coarse nystagmus of this eye. Muscular weakness and anesthesia to touch, pain and temperature of the right side were present. The corneal reflexes were absent. There was no swelling of the optic disks. The patient was completely deaf in the right ear.

Course of Illness.—A diagnosis was made of tumor of the pons, contraindicating operation. After the patient's discharge from the hospital, her symptoms increased in severity, and death occurred in May, 1913, about one and one-quarter years from the time of the onset of the symptoms. A partial necropsy was made.

Necropsy.—The pons was replaced by a firm, gray tumor which invaded the subarachnoid spaces and completely covered the anterior portion of the pons. It extended from the crus above down through the olive. The fourth ventricle was crowded back. This bulky tumor grew down to cover the base of the medulla and filled up both cerebellopontile angles (fig. 13). The basilar vessels were imbedded deeply in the tumor.

Comment.—This represents another case diagnosed as tumor of the pons and considered to be inoperable. The tumor, as in other examples of this type, extended from the pons to fill out the adjacent cerebellopontile angle.

Fig. 15 (case 9).—This unipolar spongioblastoma, as did the tumor in case 8, grew out over the base of the pons to overly the medulla and fill in the left cerebellopontile angle.

CASE 9.—*Onset with occipital headaches and blurring of vision. Diplopia. Loss of sensation over right side of body. Presumed tumor of cerebellum. Subtemporal decompression. Suboccipital exploration, with negative results. Death. Necropsy disclosed tumor of pons and cerebellum.*

Clinical History.—Mrs. Preston J. was admitted to the Johns Hopkins Hospital on July 23, 1908, for observation. The present illness began five months before admission with severe occipital headaches and blurring of vision. Two weeks later, diplopia was noted. Three months after the onset, the patient was advised to have her glasses changed to correct her failing vision. There soon developed numbness spreading over the entire right side of the body. There was no nausea or vomiting.

Physical Examination.—The patient was well nourished. There was paralysis of the left abducens nerve. The sensation over the right side of the body was impaired, and in addition there was slight weakness of the right hand and arm. A slight swelling of the left optic disk was seen.

Course of Illness.—The diagnosis was not clear, and a subtemporal decompression was made on July 24, 1908. There was a steady progress of symptoms with signs of increasing intracranial pressure. Annoying attacks of hiccup, gradual paralysis of the right side, dysarthria and involvement of the right abducens nerve brought the patient back to the hospital. On Oct. 24, 1908, a suboccipital exploration was made, but a tumor was not disclosed. The patient died three weeks later. A partial necropsy was allowed.

Necropsy.—The dorsal and basilar portion of the left half of the pons was replaced by a firm, gray-yellow tumor containing many small cysts. This tumor extended into the left cerebellopontile angle and also formed a tongue of tissue over the medulla oblongata (fig. 15).

CASE 10.—*Onset with paralysis of left sixth nerve and diplopia. Six months later, deafness in left ear; then in right ear. Tinnitus. Paralysis of left seventh nerve. Dysarthria. Staggering gait. Suboccipital headaches. Neurofibromatosis. Diagnosis: Left acoustic tumor. Negative results in suboccipital exploration. Early and sudden fatality. Necropsy.*

Clinical History.—On June 4, 1919, Elsie T., aged 29, was referred for observation. The illness began about two years before admission with paralysis of the left external rectus muscle and diplopia. About six months later, deafness began in the left ear, and soon involved the right ear. There was no tinnitus. About the same time, twitching of the left facial muscles began, and left facial paralysis developed. Suboccipital headaches, dysarthria, staggering gait and dysphagia appeared during the year before admission.

Physical Examination.—Paralyses of the motor division of the left fifth and of the sixth and seventh nerves were present. Deafness was complete in the left ear. There was nystagmus on looking to the left and right. Weakness and hypotonicity of both lower extremities were noted, and ataxia of both upper extremities, both more marked on the right side. The Romberg test was positive, and the patient fell to the left. There were generalized subcutaneous neurofibromas over the legs and back and multiple pigmented areas in the skin over the back and neck. Symptoms of general pressure were not present.

Course of Illness.—A preoperative diagnosis of acoustic tumor was made, and a suboccipital exploration was undertaken. Internal hydrocephalus was demonstrated, but a tumor was not seen. There was an early postoperative fatality.

Necropsy.—The medulla was found to be wedged into the foramen magnum. The pons was enlarged, and in the subarachnoid spaces was a spreading glioma which crossed the median line to involve the fifth to the twelfth cranial nerves on the left side and the sixth nerve on the right side. The coronal sections disclosed a firm tumor replacing the greater part of the left side of the pons and left cerebellar hemisphere and filling in the left cerebellopontile angle. Several recent hemorrhages into the tumor were seen (fig. 16).

Comment.—In this patient, the presence of the subcutaneous nodules and pigmented lesions associated with the symptoms and signs of a lesion in the posterior fossa suggested that the tumor was an acoustic neurinoma. Neurofibromas and pigmented areas in the skin of the

trunk have been found in a certain number of patients with acoustic neurinomas, in patients with gliomas in the region of the optic chiasm and third ventricle and in one patient with a verified fibrillary astrocytoma of the pons.

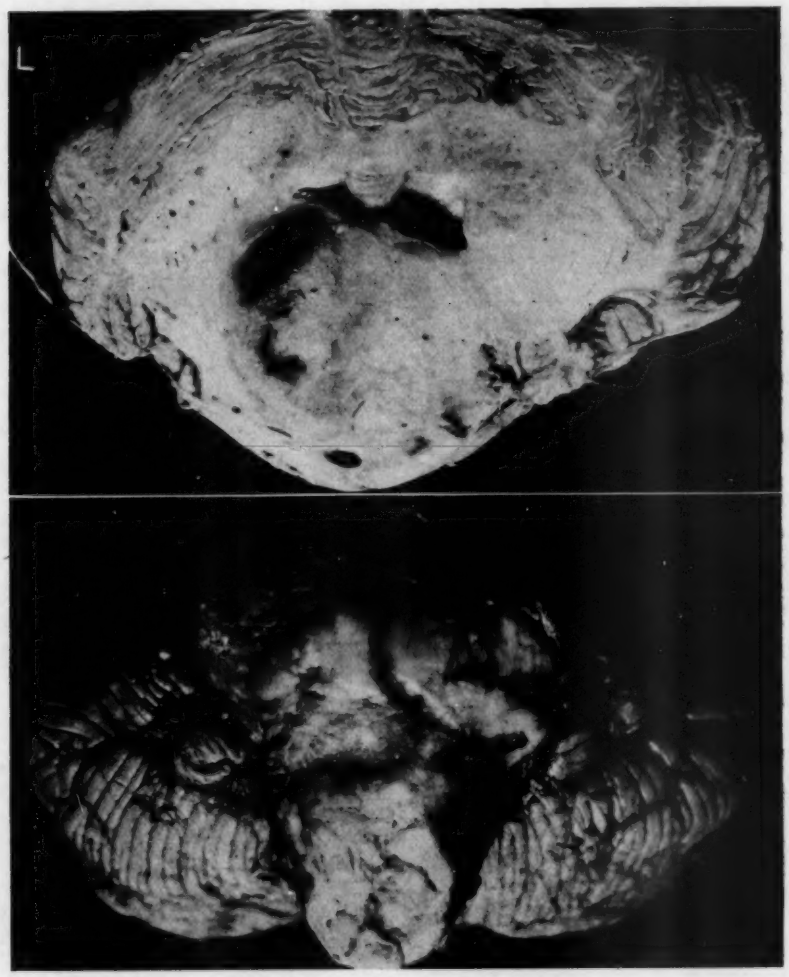

Fig. 16 (case 10).—This unipolar spongioblastoma filled out the left cerebellopontile angle and gave the symptoms suggesting an acoustic neurinoma. The coronal section shows the basilar artery buried in the tumor.

ASTROCYTOMAS

Astrocytomas are classified as either of the fibillary or of the protoplasmic type. There are 109 examples of fibrillary and eighty-five protoplasmic astrocytomas among the 721 verified gliomas.

Fibrillary astrocytomas are found with about equal frequency in the cerebellum and in the cerebrum. In the hospital series, fifty-two were located in the cerebellum, and thirty-eight of these were found in children under 15 years of age. The patients with such a lesion in the cerebral hemispheres were mostly adults.

Protoplasmic astrocytomas are usually found in the cerebral hemispheres, only eighteen of eighty-five verified cases having been found in the cerebellum. Fourteen of these eighteen tumors located in the cerebellum occurred in children under 15 years of age. Of the sixty-seven patients with such a lesion in the cerebrum, sixty-three were adults.

Both types of astrocytomas are considered to be slow growing, with a varying period from the onset of symptoms to the point of hospitalization. Because of the location of the astrocytomas in the cerebellum and because of their occurrence more especially in childhood, more than one half of the patients had symptoms for less than six months before operation, the tumors in the remainder going from one to several years before coming to operation.

Both protoplasmic and fibrillary astrocytomas are most commonly found in the midcerebellar region arising from the posterior part of the roof of the fourth ventricle. Of seventy such verified tumors, fifty were located in the fourth ventricle, and the greater number of these were cystic. The other twenty were located in one or the other hemisphere of the cerebellum and some of them jutted into the fourth ventricle. In the cystic astrocytoma, the tumor existed as a mural nodule.

There are nine examples of tumors of the astrocyte type, six of which are classified as of the fibrillary type, two as of the protoplasmic variety and one as an astroblastoma.

It is of clinical interest that five of these nine astrocytomas were included among the eight tumors suspected of being acoustic which were found among the twenty-five cases included in this report. The special clinical features will be mentioned in the comments on each case.

The six examples of astrocytoma fibrillare were found in patients 9, 12, 14, 28, 42 and 48 years of age. The duration of life from the onset of symptoms until the fatal termination was 6, 8 and 11 months, 2½, 3 and 4 years, respectively.

One of these six patients died shortly after admission, and four of the other patients died following suboccipital exploratory operations: one patient, not operated on, died at home.

The gross lesions in these six cases differed in that four involved the dorsal portion of the pons alone, and the tumors were not seen until coronal sections of the pons were made (figs. 19 and 21). These

four astrocytomas were not large, but their location in obstructing the fourth ventricle resulted in a hydrocephalus and an early fatal result (fig. 20). The remaining two examples of fibrillary astrocytoma involved one side of the pons, the adjacent brachium pontis and cerebellar hemisphere and then filled in the cerebellopontile angle on that side. Clinically, these two tumors simulated acoustic tumors.

The cut surface of all the fibrillary astrocytomas showed them to be tough and gray-white, with small cysts and but little opaque, necrotic tissue.

The two examples of protoplasmic astrocytoma occurred in adults 33 and 43 years of age. Both patients were suspected of having an acoustic tumor, and in each, the tumor was found involving the pons, adjacent cerebellar hemisphere and cerebellopontile angle.

The microscopic structure of the fibrillary and protoplasmic astrocytomas showed no differences from that of similar tumors elsewhere in the brain. They were all invasive, and all presented various aspects of necrosis. In the fibrillary astrocytomas, multiple small and large cysts were common. In this type of glioma, as in the unipolar spongioblastoma, the nerve fiber tracts showed much less damage than in such gliomas as glioblastoma multiforme. In the fibrillary astrocytoma, in the midst of the tumor, it was possible to find intact nerve cells of cranial nerve nuclei, as well as myelinated and unmyelinated nerve fibers. In the necrosis associated with glioblastomas, fiber tracts were totally destroyed. The reaction to the slow-growing tumors, such as the astrocytomas, was much less marked than that to the rapidly growing, extensively necrotic glioblastomas.

The histories of five patients with either fibrillary or protoplasmic astrocytoma or astroblastoma will be presented.

The tumor in case 1 (fig. 17) was one of four examples of fibrillary astrocytoma involving the pons alone. The pars dorsalis appears to be principally involved by this tumor (fig. 17). Special involvement of the basilar portion of the pons is illustrated in figure 18.

The remaining cases of fibrillary and protoplasmic astrocytoma and astroblastoma illustrate gliomas involving the pons, adjacent cerebellar hemisphere and cerebellopontile angle. Clinically, the patients with these tumors were suspected of having acoustic tumor.

CASE 11.—*Onset with paralysis of third nerve. Right hemiplegia. Weakness of right side of face. Symptoms of general pressure. Exploratory craniotomy with finding of increased pressure. Early fatality. Necropsy disclosed tumor of pons.*

Clinical History.—On July 27, 1911, Hortense H., aged 12, was admitted to the Johns Hopkins Hospital for observation. Four years before the patient's admission, the parents noticed that the child's left eye was turned up and out. Soon a weakness, followed by paralysis of the extremities of the right side, began.

One year later, a weakness of the right facial nerve was noticed. In the year before admission, symptoms of general pressure were evident. The gait became unsteady. There was no tinnitus. Despite the previous developments, the child went to school and was able to read well until the time of admission.

Physical Examination.—The child was hydrocephalic. Both optic disks were swollen to 4 diopters. There was a paralysis of the right third nerve and facial weakness on the right. There was weakness of the right trapezius and hypesthesia to pain, touch and temperature over the paralyzed right side. The abdominal reflexes were absent. A bilateral Babinski reflex and ankle clonus on the right side were brought out.

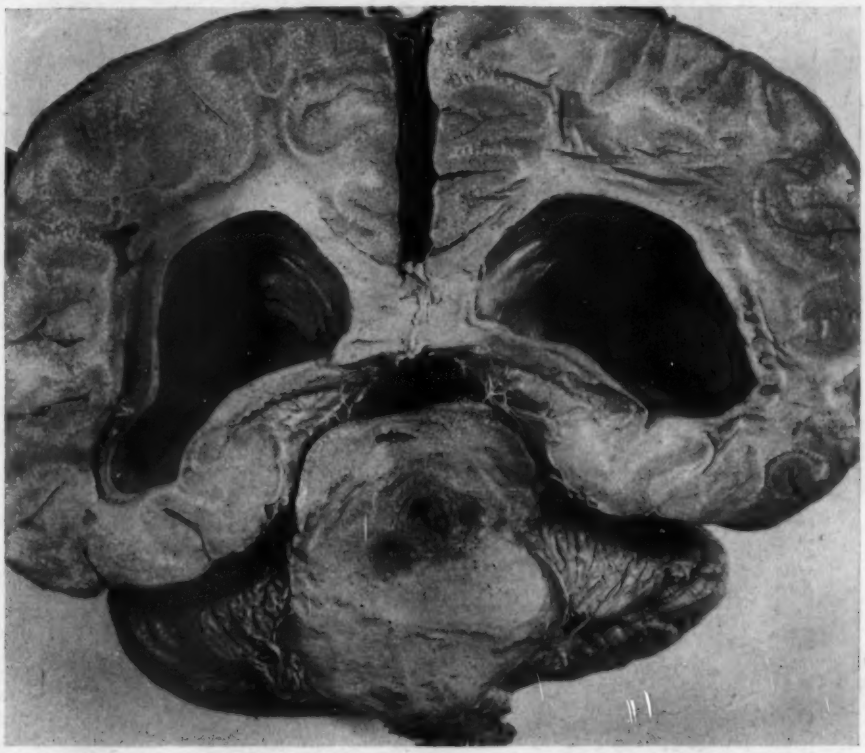

Fig. 17 (case 11).—The dorsal part of the pons appears to be especially involved by this fibrillary astrocytoma. The fourth ventricle is represented by a mere slit, and there is resultant dilatation of the lateral ventricles.

Course of Illness.—Four days after admission, an exploratory operation disclosed ventricular fluid under great pressure. Owing to the development of respiratory embarrassment, the exploration was abandoned. Death occurred twenty-four hours after operation. Necropsy was performed.

Necropsy.—The pons was asymmetrically enlarged, but the external appearance did not suggest a tumor. A series of coronal sections showed a tumor involving the dorsal part of the pons and obliterating the aqueduct of Sylvius with a resultant hydrocephalus (fig. 17). The tumor extended forward to the left side

of the third ventricle and filled the interpeduncular space. It then bulged beneath and into the left optic thalamus to project across the midline to block the right foramen of Monro. The entire tumor was a uniform gray, except for small central yellow areas of degeneration.

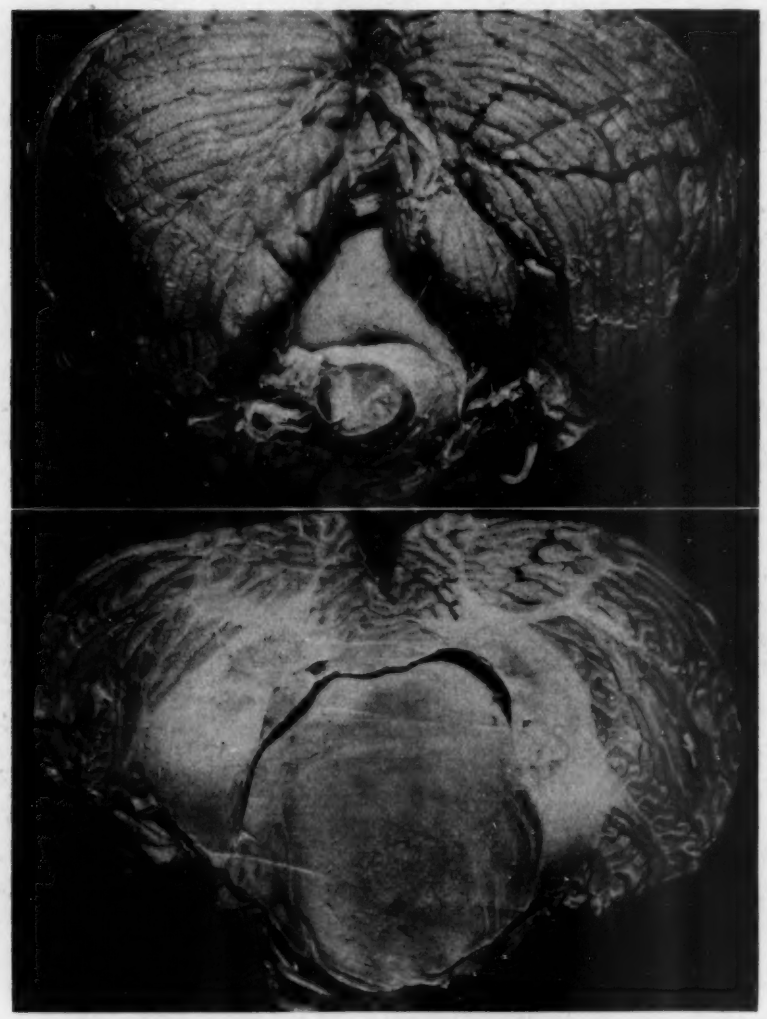

Fig. 18.—The diffuse enlargement of the pons by the fibrillary astrocytoma caused a complete occlusion of the fourth ventricle by projecting into it, in contrast to the compression of this ventricle as seen in figure 17. In the upper figure, the solid tumor of the pons is seen to project between the tonsils of the cerebellum.

Comment.—This diffuse fibrillary astrocytoma was confined to the pons and invaded the cerebral penduncles. The cerebellum was not involved.

CASE 12.—*Gradual but incomplete development of deafness (right). No tinnitus. Involvement of right fifth, sixth, seventh and eleventh nerves. Cerebellar signs and symptoms. Suboccipital exploration with exposure of supposed tumor of medulla. Death two months later. Necropsy disclosed tumor of pons.*

Clinical History.—On Sept. 16, 1927, George G., aged 42, was referred for observation. For nineteen years, the patient was aware of the gradual development of deafness, without tinnitus, in his right ear. There were no other neuro-

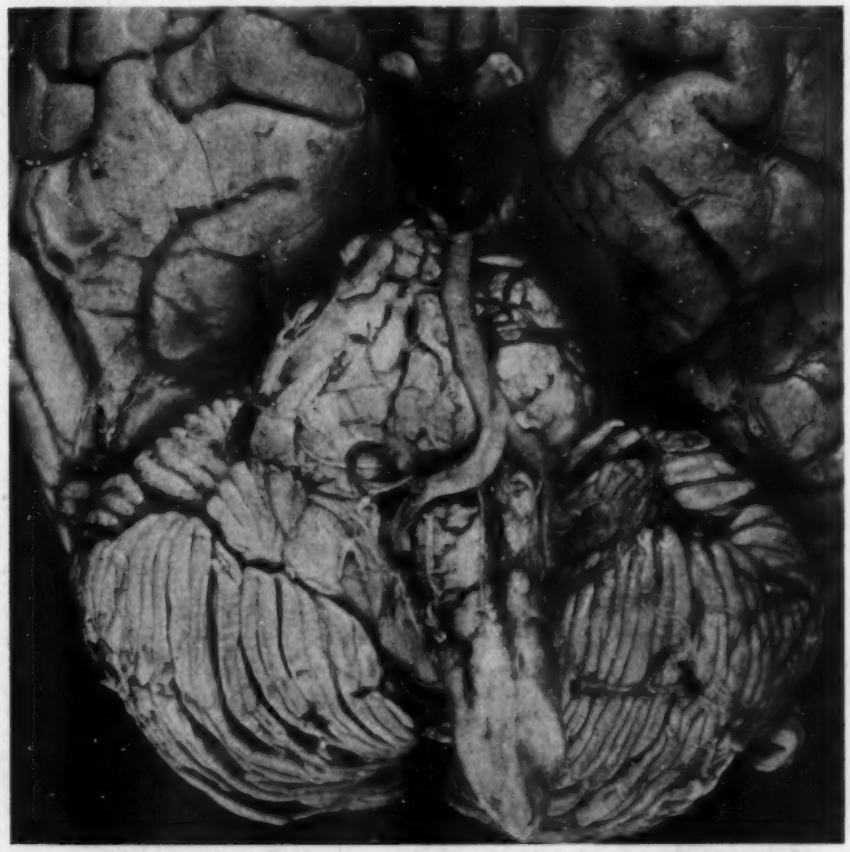

Fig. 19 (case 12).—Except for the distortion of the right vertebral and basilar arteries and the fullness of the right lateral recess, a tumor would not have been expected.

logic symptoms until two and a half years before admission, when numbness of the gums about the right upper molar teeth annoyed the patient to such an extent that he had these teeth extracted. The loss of sensation over the area of the fifth nerve spread until the entire right side of the face was numb. About the same time, involvement of the right facial nerve was manifested by twitching of the facial muscles. Two years before admission, dizziness and staggering gait began. The equilibrium of the right leg was especially involved, and he staggered to the right side. Several months later, daily attacks of vomiting began and lasted

until admission. In the next eighteen months, there developed diplopia on looking to the right, a feeling of thickness of the tongue with consequent difficulty in speech, difficulty in swallowing and increased irritability. There was no history of tinnitus or of visual disturbance other than diplopia. Only occasionally were there occipital headaches during a short period before admission.

Physical Examination.—The right fifth (sensory division), sixth, seventh, eighth and eleventh cranial nerves were involved. The deafness in the right ear was incomplete. There was a pronounced nystagmus, even at rest, rapid on deviation to the right and slow on deviation to the left. The optic disks appeared normal. The ataxia and hypermetria of the right leg, the positive Romberg test with falling to the right, the staggering gait and the dysarthria suggested a lesion in the posterior fossa, most probably a slow-growing tumor of the cerebellum.

Course of Illness.—On Sept. 29, 1927, a suboccipital exploration revealed what appeared to be a tumor of the medulla. After the operation, a severe pulmonary

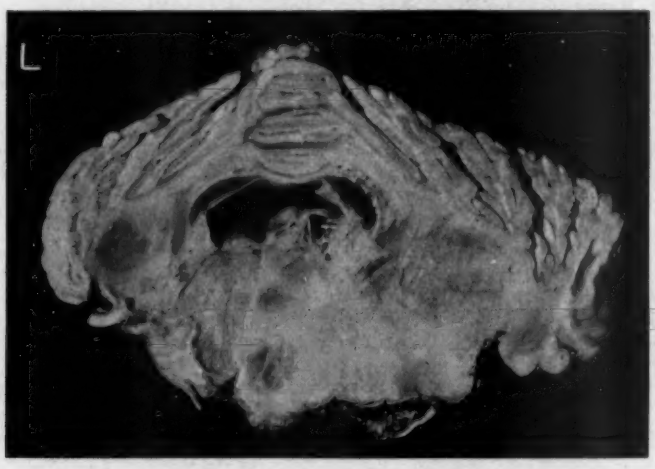

Fig. 20 (case 12).—This coronal section through the fibrillary astrocytoma seen in figure 21 shows the involvement of the pons and cerebellum.

lesion, either an abscess or a necrotizing pneumonia, proved overwhelming, and death occurred on Nov. 29, 1927.

Necropsy.—The left half of the pons and medulla appeared normal, but the right side of the pons was asymmetrically enlarged by a dense tumor which did not appear to have invaded the subarachnoid spaces (fig. 19). The bulging tumor partly filled the right cerebellopontile angle. The right fifth to eleventh cranial nerves, inclusive, were distorted and out of their normal positions. The coronal sections of the brain stem showed a dense, nondemarcated, gray-white, finely multicystic tumor, which replaced a portion of both the dorsalis and the basilar portion of the right side of the pons, the brachium pontis and cerebellar hemisphere. The fourth ventricle was compressed and distorted (fig. 20). The fibrillary astrocytes making up the tumor are shown in figure 21.

Comment.—There were several facts against the diagnosis of an acoustic tumor. The negative caloric tests and the incomplete deafness and absence of tinnitus made such a lesion improbable, although in

some cases of verified acoustic neurinoma the deafness has been found to be incomplete. The absence of the evidence of increased intracranial pressure was a further point against the presence of an acoustic neurinoma.

CASE 13.—*Onset with dizziness. Mastoidectomy followed by facial paralysis on the right. Unsteady gait. Late symptoms of general pressure. Weakness and unsteadiness of the right side. Suboccipital exploration, with early fatality. Necropsy disclosed tumor of pons.*

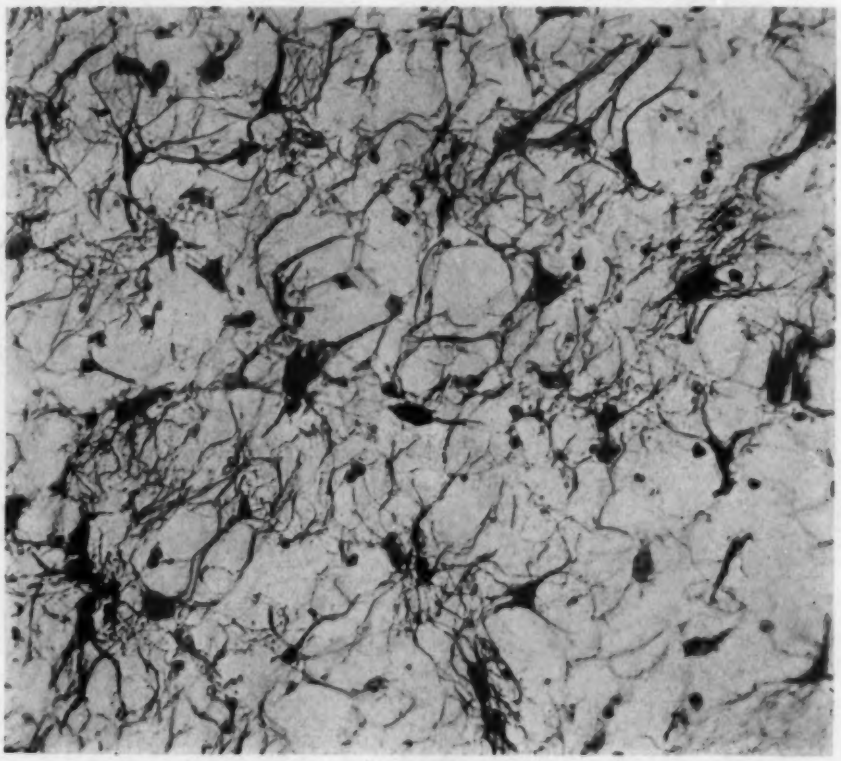

Fig. 21 (case 12).—Fibrillary astrocytoma; stained with phosphotungstic acid hematoxylin; × 300.

Clinical History.—On May 28, 1915, Carrie P., aged 48, was referred for observation. The illness began in August, 1913, with dizziness. After an interval, mastoidectomy was performed, with no change in the symptoms. Facial paralysis on the right developed soon after this operation. Within a year, an unsteady gait complicated the now persistent dizziness, and the patient frequently fell to the right side. In the several months before admission there occurred in rapid succession suboccipital headaches, nausea and vomiting, tinnitus (left), weakness and unsteadiness of the right arm and leg, dysarthria and dysphagia. There was no deafness.

Physical Examination.—The patient was unable to walk and fell to the right and back when held up. The right pupil was smaller than the left. There was nystagmus in all directions, and a paralysis of the right seventh nerve of the peripheral type and involvement of the sensory portion of the right fifth nerve. Ataxia and dysmetria of the right arm were present.

Course of Illness.—A preoperative diagnosis of cerebellar tumor was made. A suboccipital exploration was made on June 2, 1915, and in the right cerebellopontile angle, a cyst full of yellow fluid was evacuated. The patient improved remarkably and was discharged, able to walk normally and with improved vision. One year later, in July, 1916, a severe recurrence of her previous symptoms necessitated readmission. The posterior fossa was reexplored, and again a large and similar cyst was found. After the operation, the patient failed to improve, and death occurred on July 23, 1916. Necropsy was performed.

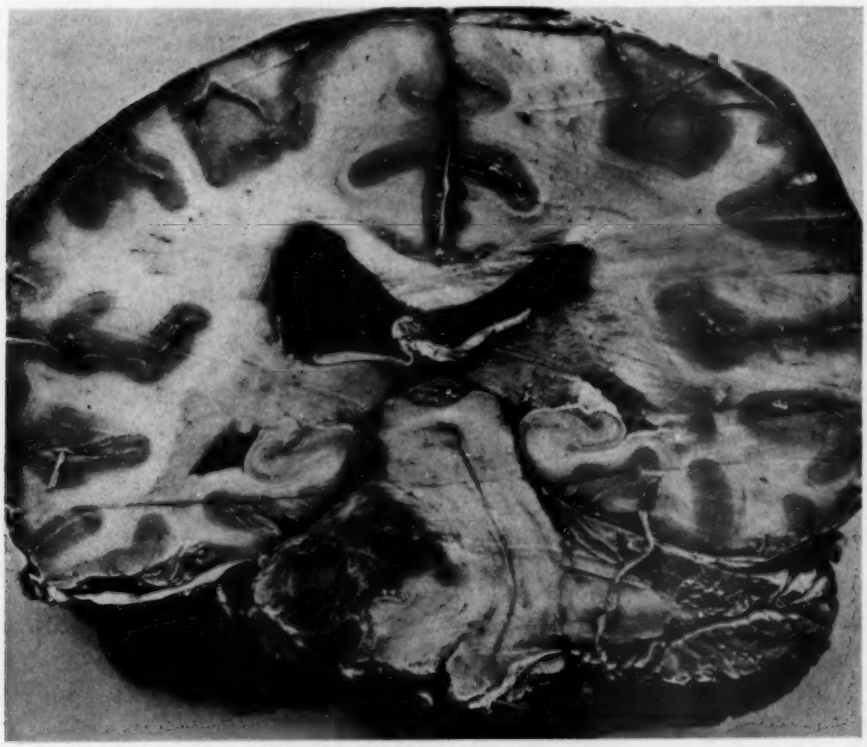

Fig. 22 (case 13).—This large, cystic, fibrillary astrocystoma was operated on twice. It filled out the right cerebellopontile angle and invaded the pons and right cerebellar hemisphere.

Necropsy.—The right cerebellopontile angle was filled with a dense tumor which extended from the right upper lateral portion of the pons and invaded the brachium pontis on the right side (fig. 22). The sections showed a dense, gray-white, translucent tissue partially replaced by multiple adjacent small and large cysts filled with gray-yellow gelatinous masses or thin yellow fluid.

Comment.—This large, cystic, fibrillary astrocytoma involved the greater part of the right cerebellar hemisphere, the brachium pons and a portion of the pars dorsalis of the right side of the pons. The onset with dizziness, followed by unsteady gait, and the great involvement of the cerebellar hemisphere suggested that this tumor originated in the cerebellum.

CASE 14.—*Gradual increase of deafness until complete (1917-1923). No tinnitus. Symptoms of general pressure. Involvement of right fifth, sixth and seventh cranial nerves. Unsteadiness of gait and staggering to right. Cerebellar exploration (1924) for presumed acoustic neurinoma with finding of tumor in right lateral recess. General improvement. Early recurrence of symptoms. Second cerebellar exploration, 1926. Temporary improvement. Death on June 8, 1927. Necropsy.*

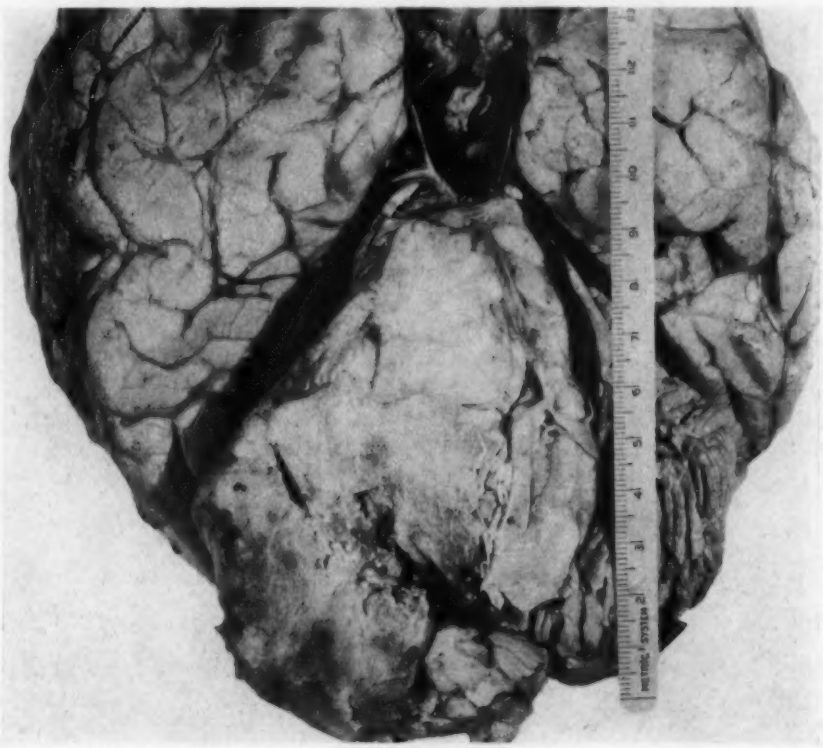

Fig. 23 (case 14).—This large cystic protoplasmic astrocytoma was operated on twice. The tumor involved the right side of the pons and the right cerebellar hemisphere.

Clinical History.—On Feb. 18, 1924, Harold L., aged 33, was referred with a diagnosis of tumor of the brain. The patient realized in 1917 that he was slightly deaf. This condition progressed to complete deafness of the right ear in 1923. There was no tinnitus. Shortly before complete deafness was present, he

had severe generalized headaches followed by dimness of vision and numbness over the right trigeminal field. Unsteadiness in gait was noticed first three months before admission.

Physical Examination.—The patient staggered to the right and walked with a wide base. There was a papilledema of 3 diopters on the right and of 5 diopters on the left. A paralysis of the right abducens nerve, a complete loss of sensation over the right trigeminal area and complete deafness in the right ear were found.

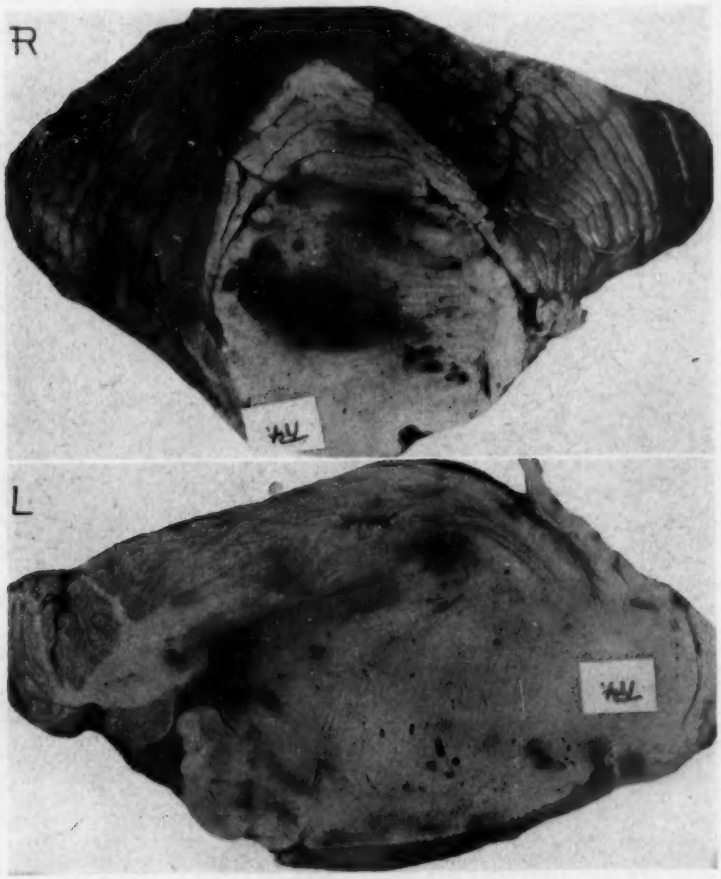

Fig. 24 (case 14).—The coronal sections of the tumor seen in figure 23, show a soft, necrotic tumor filling in the fourth ventricle and the adjacent cerebellopontile angle.

Course of Illness.—A preoperative diagnosis of right acoustic neurinoma was made. In suboccipital exploration on Feb. 26, 1924, a soft gray mass was found in the right lateral recess. There was some improvement after the operation, and a series of x-ray treatments was given. The patient was able partially to resume his legal practice until there was a severe recurrence of his previous symptoms, six months after the operation. During the next eighteen months there were fre-

quent exacerbations and partial remissions of the symptoms until the persistent bulging of the decompression area made the patient seek readmission. On April 6, 1926, in a second cerebellar exploration, a large cyst and a dense tough tumor were exposed in the right lateral recess. Again there was a temporary subsidence of symptoms, and the patient was again able to carry on some of his work for the next year until the symptoms of increased pressure made him a bed-patient. Death occurred on June 8, 1927, about ten years from the time the patient first noticed the beginning of deafness.

Necropsy.—Necropsy was performed by Dr. N. Winkleman of Philadelphia. The base of the brain stem was obscured by the large, soft, cystic mass which

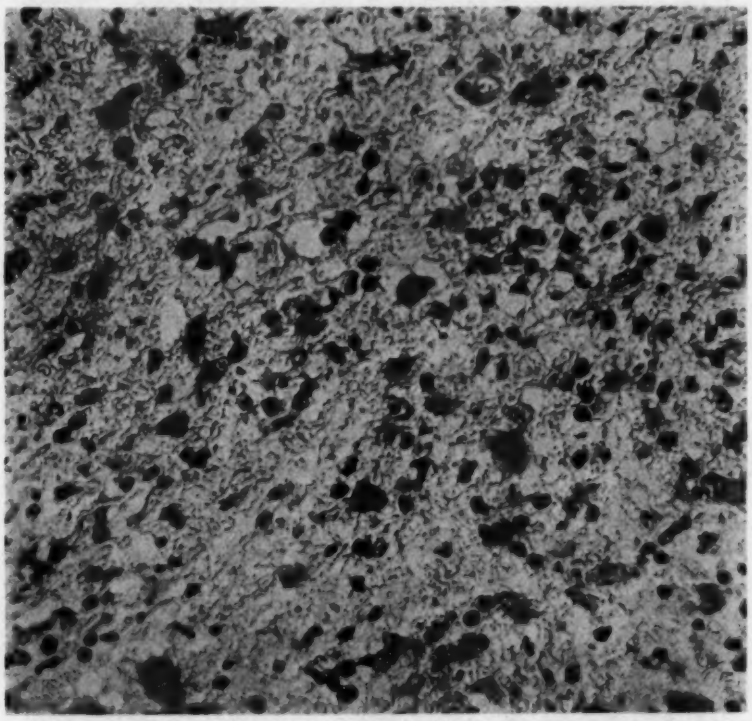

Fig. 25 (case 14).—Protoplasmic astrocytoma; stained with hematoxylin and eosin; × 300.

extended over the medulla and filled especially the right cerebellopontile angle (fig. 23). The right basilar portion of the pons, the right brachium pontis and the right side of the cerebellum were especially involved by the soft, gray-white tumor in which there were many small hemorrhages (fig. 24).

Comment.—This patient was supposed without doubt to have a right acoustic neurinoma. Although the chronology was correct, the patient was in better physical condition than a patient with an advanced acoustic tumor usually is.

It seemed remarkable that a tumor involving the pons and the cerebellum could exist and produce symptoms for a period as long as ten years. The fact that the patient lived for four years after the first operation illustrates the slow growth of this type of astrocytoma (fig. 25).

Among the eight cases of this series of cerebellopontile gliomas causing clinical symptoms and signs suggesting the presence of an

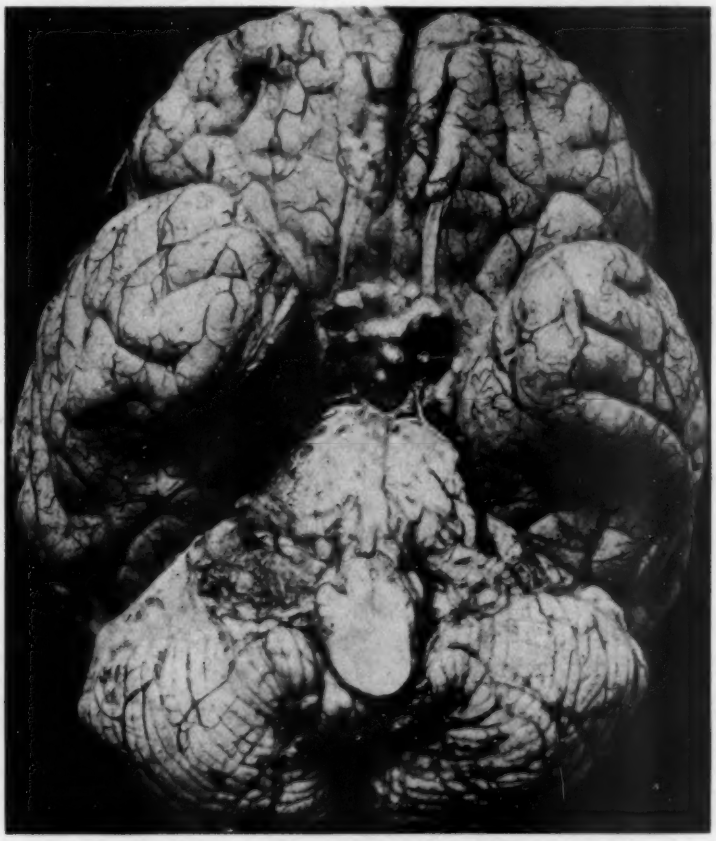

Fig. 26 (case 15).—This astroblastoma filled out the right cerebellopontile angle and involved the cerebellar hemisphere more than it did the pons.

acoustic neurinoma, this was the one considered as the most likely to be a case of acoustic neurinoma.

CASE 15.—*Onset with staggering gait, dizziness, ataxia. Soon convulsive attacks (cerebellar type). Involvement of right fifth and seventh cranial nerves. Intracranial aneurysm suspected. Rapid progress of symptoms with development of increased intracranial pressure. Considered as lesion of cerebellopontile angle. Sudden death. Necropsy disclosed tumor of pons and cerebellum.*

Clinical History.—On Sept. 20, 1927, Elizabeth H., aged 59, was admitted for the second time, having been first referred for admission on Aug. 11, 1927. The present illness began with a staggering gait about two months before the last admission. Soon numbness of the right side of the face and dizziness developed. Eleven days after the onset, the patient had a sudden convulsion characterized by marked opisthotonic clonic movements of the lower extremities and unconsciousness for twenty minutes.

On the first admission on Aug. 11, 1927, there were found a positive Romberg test, ataxia of the right hand and foot and slight deafness. The eyegrounds showed no abnormal changes. It was believed that the patient had had a small hemorrhage from an intracranial aneurysm, and she was discharged five days later, untreated.

In the five weeks' interval to the second admission, the patient had had seven recurrent convulsive attacks. Complete facial palsy on the right and difficulty in

Fig. 27 (case 15).—The coronal sections of the tumor seen in figure 26 show a soft, necrotic tumor filling in the fourth ventricle and the adjacent cerebellopontile angle.

speech and swallowing developed. Persistent nausea and vomiting were present the three weeks before admission.

Physical Examination.—There was evidence of recent loss of weight. Both optic disks showed a choking of from 4 to 5 diopters' elevation on the right and of 2 diopters' elevation on the left. There was complete deafness in the right ear. The caloric tests indicated a nerve lesion on the right. Complete facial palsy on the right of the peripheral type and involvement of the sensory division of the right trigeminal nerve were found. Persistent nystagmus, coarser to the right, gross dysarthria, marked ataxia and hypermetria in the right hand and leg, stiffness of the neck and right suboccipital tenderness were additional observations.

Course of Illness.—It was believed that a lesion of the right cerebellopontile angle was present. Two days after admission, while being prepared for operation, the patient suddenly had respiratory failure and died.

Necropsy.—An examination limited to the head was made. In the right cerebellopontile angle was the surface extension of a soft, yellow tumor involving both the pons and the right hemisphere of the cerebellum. The fifth, seventh and eighth cranial nerves on the right side were embedded in tumor (fig. 26).

The coronal sections through the cerebellum and brain stem showed a large, soft, nonencapsulated tumor replacing the ventral portion of the right hemisphere of the cerebellum filling up the greater part of the right cerebellopontile angle and invading the right lateral portion of the basilar area of the pons (fig. 27).

The microscopic sections showed it to be an astroblastoma.

Comment.—This represented the eighth case of the twenty-four in this series considered as cerebellopontile angle lesions, resembling acoustic neurinoma. However, there were many facts against this lesion's being an acoustic neurinoma. The short course of the illness suggested a metastatic lesion to the brain, but on examination there was no evidence of a primary focus. The fact that staggering gait, ataxia and dizziness were the early symptoms and that deafness occurred relatively late in the course suggested that the lesion began in the cerebellum and involved the cerebellopontile angle later. The repeated convulsive attacks with rigid neck, unconsciousness, and opisthotonic and clonic convulsions of the extremities suggested a cerebellar lesion and also a rupture of an intracranial aneurysm.

From the examination of the gross lesion it would seem that the tumor began in the ventral portion of the right hemisphere of the cerebellum, grew to fill out the angle and then involved only the lateral area of the basilar portion of the right side of the pons.

COMMENT

This study was made for the purpose of classifying these gliomas of the pons and of the pons and cerebellum, and a discussion of the clinical symptoms will not be presented.

Horrax [7] analyzed the clinical observations of fourteen patients of this group of pontile gliomas and called attention to the frequent involvement of the cranial nerves, especially of the oculomotor group, both at the onset of the illness and during the course of it. He also commented on the frequency of psuedocerebellar signs and symptoms, but the study of the gross specimens of these tumors indicates that these clinical manifestations were due to the involvement of the cerebellum.

Eight of the patients with pontile gliomas were suspected of having tumors of the acoustic nerves, and in each there was found a glioma involving a portion of the pons and the adjacent cerebellar hemisphere and filling in part of the cerebellopontile angle. A correlation of the

7. Horrax, G.: Differential Diagnosis of Tumors Primarily Pineal and Primarily Pontile, Arch. Neurol. & Psychiat. **17**:179, 1927.

clinical and pathologic observations in these patients will form a separate communication from Dr. Horrax and myself.

Pathology.—Although these tumors were considered as "gliomas of the pons" for statistical and localizing purposes, it was found from the study of the gross specimens that in but four instances was the pons alone the site of the tumor. In each of these four instances the tumor was a fibrillary astrocytoma involving the pars dorsalis of the pons and either compressing the aqueduct of Sylvius and the fourth ventricle or actually growing up into the fourth ventricle; the pons was symmetrically enlarged, and a tumor would scarcely have been suspected from the external appearance.

In the remaining twenty gross specimens, the tumor involved one or the other side of the pons or both and the adjacent brachium pontis and hemisphere of the cerebellum. In all these specimens, the tumor filled in one or the other cerebellopontile angle, and clinically many of the patients were considered as having tumor of the cerebellum or tumor in the cerebellopontile angle.

The gross structure of the gliomas considered varied with their type. All the examples of glioblastoma multiforme and the one of astroblastoma were large, soft tumors with many areas of necrosis, hemorrhage and cyst formation. These tumors involved the base of the pons especially. Consequently, the basilar artery and its branches were embedded in the soft growth, and the brain stem was given a corrugated appearance. The ten examples of glioblastoma multiforme and the one of astroblastoma represent the only examples of such types of glioma found in the brain stem or cerebellum among all the varied tumors observed in this clinic. There would seem to be no reason why such gliomas should not be located in either the pons or the cerebellum.

The unipolar spongioblastomas and the fibrillary astrocytomas were small, tough, invasive tumors containing cysts of varying size, and they were altogether different in their gross appearance from glioblastoma multiforme.

Histologically, these tumors showed no essential differences from similarly classified tumors seen elsewhere in the brain. The sections taken from the periphery of the tumor in the pons gave a confusing picture because of the interlacing of the fiber tracts. The cells of glioblastoma multiforme and spongioblastoma unipolare tended to grow along the tracts.

In the central portions of the rapidly growing glioblastomas, the necrosis of the nerve tracts and ganglion cells was such that none or little of these tissues was left. In contrast, the study of the central portions of the slower growing gliomas in this group showed some intact nerve fibers, axis cylinders and ganglion cells. The tumor cells

could be seen invading the perineural spaces and undergoing mitosis there at the advancing edge of the glioblastomas. Intact ganglion cells were often seen surrounded by the infiltrating astrocytoma and spongioblastoma unipolare.

The reaction of the brain toward the invading tumors differed. At the periphery of the rapidly growing glioblastoma and at that of the one astroblastoma, with all of the necrosis and hemorrhage, there was seen such a collection of advancing microglia in the cerebellum as to make one think of a tumor of these cells. The usual and well known changes of these cells into phagocytic cells were clearly followed. There was a much less marked response on the part of the fibrillary astrocytes. The small blood vessels in the uninvaded tissue at the periphery of these tumors frequently showed an increase in number as well as an increase in mitoses in the cells in their walls. This proliferation of cells beneath their lining often resulted in almost complete occlusion of the lumen.

The reaction of the microglia about the periphery of the astrocytoma and that of the unipolar spongioblastoma was much less marked. At the edge of the protoplasmic astrocytoma, the cells of the tumor were so mixed with a response on the part of the fibrillary astrocytes that a mixed tumor appeared to be present.

The origin of a tumor which involved the pons, brachium pontis and cerebellum could not be demonstrated in any of the gross specimens. However, in correlating the clinical and anatomic observations it was interesting to note that in the six patients giving as their first symptom staggering gait, the lesion involved one cerebellar hemisphere extensively and the adjacent portion of the pons less extensively. In the patients giving as their first symptom evidence of involvement of some of the cranial nerves, the lesion was extensive in the pons as well as in the adjacent cerebellar hemisphere.

SUMMARY

A group of tumors involving the pons and the cerebellum, previously unclassified, have been classified, as are the other gliomas verified in this clinic.

Although grouped as pontile gliomas, only four of these tumors were found to involve the pons alone; the remaining twenty-one involved the pons, brachium pontis and the adjacent cerebellar hemisphere and cerebellopontile angle. The origin of this larger group involving the cerebellum and the pons could not be demonstrated from the gross examination.

Ten of the twenty-five tumors were classified as glioblastoma multiforme. Here the average duration of life from the onset of

symptoms to the fatal termination was but four months. Each of the tumors was large, soft and necrotic, with many hemorrhages and cysts. The basilar vessels and cranial nerves were often buried in the soft, expanding tumor. The histologic structure of this rapidly growing type of glioma was similar to that found in glioblastoma multiforme of the cerebral hemispheres, except that at the periphery of the tumor the pattern of growth was modified by the invasion along the fiber tracts.

The one example of astroblastoma proved to be the only instance of such a lesion to be found in the brain beneath the tentorium.

Fourteen of the gliomas were slower growing tumors and were classified as protoplasmic, as fibrillary astrocytoma or as spongioblastoma unipolare. The gross and histologic structure of these tumors was similar to that of such tumors found elsewhere in the brain.

The average duration of life of patients of this group from the onset of symptoms to the fatal termination was two years, the extremes being four months and four years.

The reaction of the brain against the advance of tumor varied in degree. The response of glial elements, microglia, connective tissue and blood vessels was greatest at the periphery of the glioblastoma multiforme and least at the edge of the slower growing astrocytoma and spongioblastoma unipolare.

A CONGENITAL CAPILLARY ANGIOMA OF THE PAROTID GLAND

CONSIDERATION OF SIMILAR CASES IN THE LITERATURE *

JOSEPH McFARLAND, M.D.
PHILADELPHIA

While I was visiting Grace Hospital, Detroit, Dr. Clarence J. Owen showed me a tumor of the parotid gland, removed by Dr. Frank J. Kelly and received in the hospital laboratory for study and diagnosis. I recognized it as rare and interesting, and since I was known to have written on tumors of the region, Dr. Owen kindly presented it to me. I now place it on record with the full permission of Dr. Kelly and Dr. Owen.

REPORT OF CASE

History.—R. E. H., a white boy, aged 5 months, at birth was found to have a swelling "on the left side of the face, primarily back of the angle of the jaw." It increased slowly until the fifth month; then it grew larger rapidly "and extended over the angle of the jaw." It was regarded as a malignant tumor, and the patient was brought to the hospital for operation on March 4, 1929. At that time, the skin covering the area was "contracted," and the appearance suggested "a cystic disturbance below." There was no discoloration of the skin, nor was there any vascular nevus on or about the swelling.

The operation resulted in the exposure and removal of a flattened, well encapsulated mass measuring approximately 6 by 6 by 3 cm.

The child quickly recovered from the operation, and the wound healed nicely. The last examination was made about Oct. 1, 1929, nearly seven months after the operation; then the patient appeared to be well and showed a normal gain in weight.

Though seven months is a short time in which to conclude the history of any tumor, there is good reason to suppose that this was a benign disturbance of a kind not marked by recurrences, so that there is no reason to postpone further the report of the case.

Gross Appearance.—The general shape of the tumor was circular, slightly flattened and thicker at the middle than at the edges. It was enclosed in a fairly smooth, rather tough capsule. When cut across the greater diameter and then in several other directions, it was found to be of the same consistency and grayish-pink throughout, except that a few areas showed a darker reddish tint. There were no cysts or necrotic areas.

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* Submitted for publication, Nov. 13, 1929.

* From the McManes Laboratory of Pathology of the University of Pennsylvania.

The tissue was distinctly lobulated, the lobules being but a few millimeters in diameter and slightly separated from one another by narrow bands of vascular areolar tissue, and meeting one another by flattened surfaces so as to have numerous sides and various blunt and sharp angles. It thus exactly resembled the parotid gland, the only notable difference being the great size of the removed mass. It was more like a hypertrophy of the gland than a tumor.

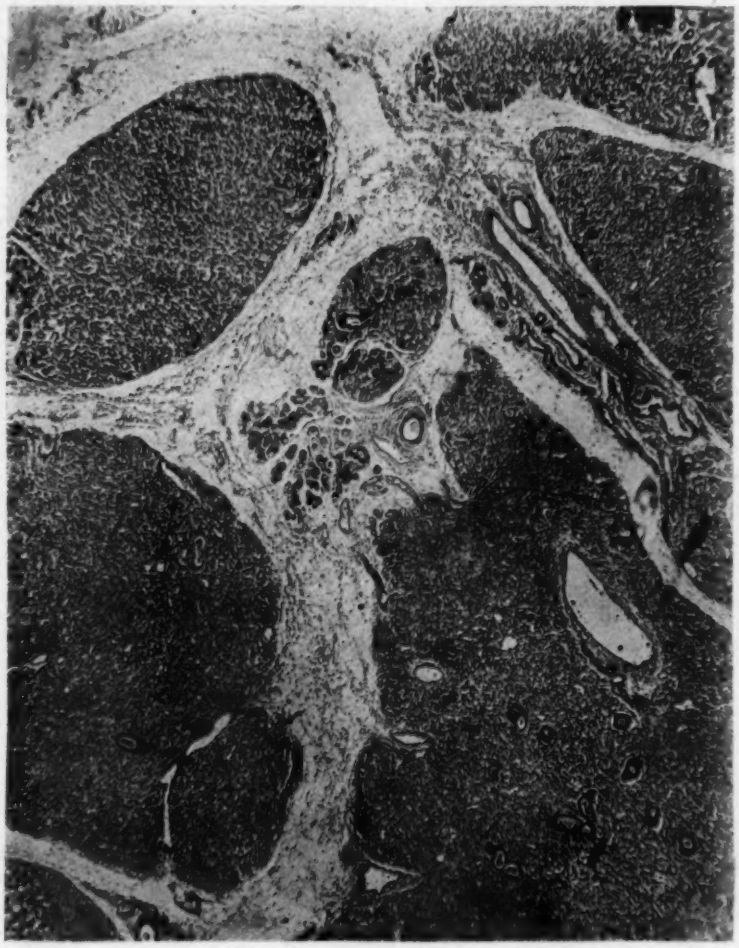

Fig. 1.—The lobular structure of the tumor is shown. Small ducts can be seen in the lobules, and larger ones between them.

Microscopic Examination.—Sections from various parts of the lesion were cut in paraffin, stained and examined. Under low magnification, the tissue showed a fairly uniform texture divided into larger and smaller lobules by intermediate bands of fibrillar tissue. An increase in the magnification (fig. 1) gave the impression that the tissue was a gland with compact acinous tissue forming the lobules, and with a duct system composed of smaller elements in the lobules

and larger ones between them. Scattered elements near the center of the illustration indicated that the organ was a racemose gland.

Observation under a still higher power, as in figure 2, yielded a surprise. The field shown in this illustration was from one of the larger lobules, near its central part. In the center there was a duct, the epithelial lining of which seemed to be made up of an excessive number of crowded cells. But about it, where the acini

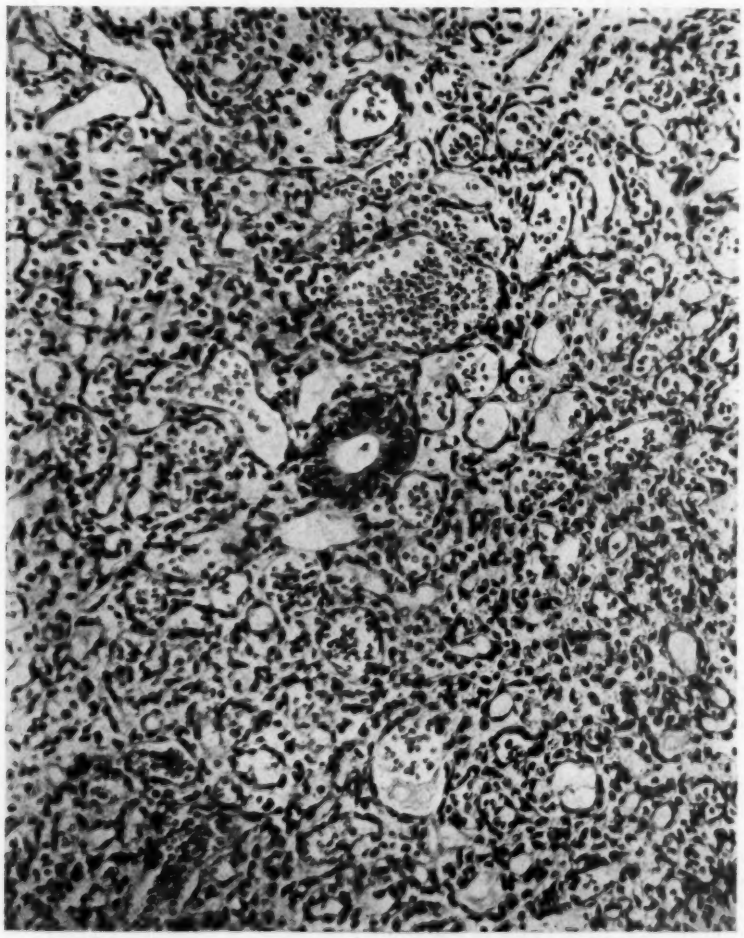

Fig. 2.—A higher magnification of one of the lobules, showing a duct in the center. There is no glandular tissue; the whole lobule is made up of vascular tissue.

of the parotid gland should have been, there was a new tissue made up of small blood vessels, in many of which the red corpuscles could be distinctly seen. If the slide was moved so as to shift the field of observation toward the periphery of the same lobule, the vessels became both more numerous and larger. Scarcely anything other than vascular tissue could be discovered. Study of numerous sections from various parts of the lesion led to the impression that throughout

the entire parotid gland, probably prior to the period of its anatomic perfection, the vascular tissue adopted an abnormal vegetative activity that resulted in an excess of capillaries at the expense of the glandular tissue, most of which did not develop, while the remainder became so crowded and compressed by the vessels as to be unrecognizable, except as scattered individual cells among the capillaries, with shapeless groups of cells here and there, as shown in figure 3.

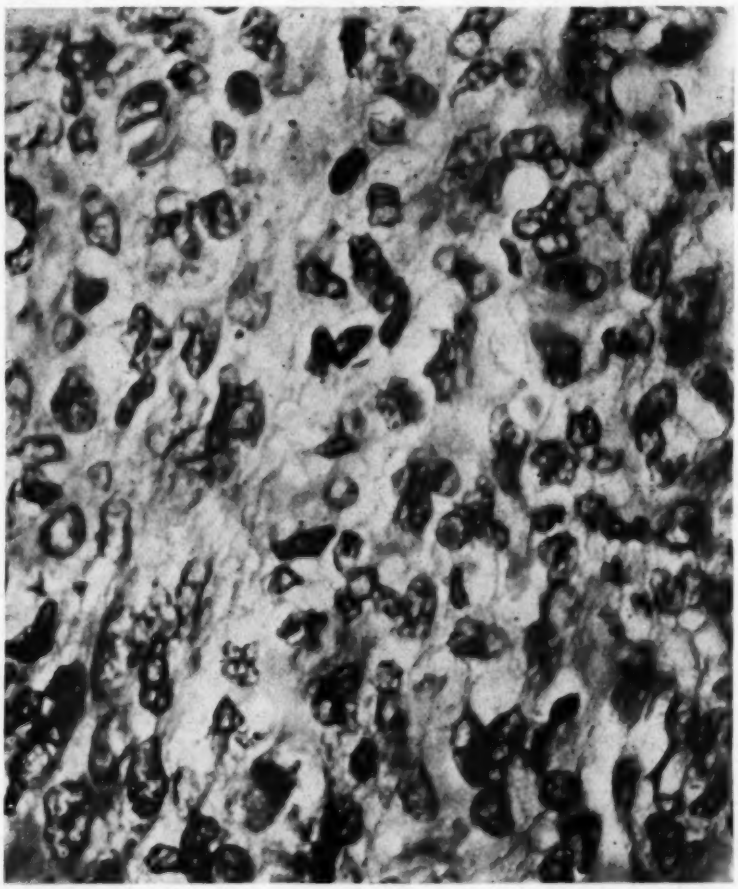

Fig. 3.—The lobule under high power, showing the ambiguous cellular structure, and the difficulty of differentiating between the growing capillary endothelial cells and the crowded and inactive epithelium.

It might not be amiss to suppose that, after birth, this undeveloped gland, unable to secrete saliva, responded to the secretory stimulations through distention and, perhaps, extension of its vessels, so that the whole diseased parotid gland rapidly enlarged.

Diagnosis.—Congenital capillary hemangioma of the parotid gland.

Reported Cases of Angioma of the Parotid Gland and Adjacent Structures

Capillary Angiomas of the Parotid Glands

No.	Reporter and Reference	Sex	Age of Patient at First Observation	Age of Patient at Subsequent Observation or Operation	Side	Treatment	Result	Size; Comment
1	Erőss: Jahrb. f. Kinderh. **19**: 345, 1882-1883	F	4 months	9 months	R	Operation	Death	Size of large nut
2	Hartman (case 1): Rev. de chir. **9**: 756, 1889	F	6 weeks	8 months	L	Extirpation	Cure	5 by 4 cm.
3	Hartman (case 2): Ibid.	F	6 weeks	5 months	L	Enucleation	Recovery	No change in the skin
4	Hartman (Tenon) (case 3): Ibid.	..	At birth	.....	..	Autopsy	Autopsy	Size of fist and limited to parotid gland
5	Hartman (Berard) (case 4): Ibid.	F	.....	3 years	R	Autopsy	Autopsy	Seemed to be a hypertrophied parotid gland
6	Hartman (Duke) (case 5): Ibid.	..	3 months	9 months	L	.....	.....	At first thought to be an aneurysm; looked like hypertrophied parotid gland
7	von Margoldt (case 1): Jahrb. f. Nat. u. Heilk. **6**: 250, 1897	M	.....	4 months	R	Extirpation	Facial palsy	Size of fist; bluish skin
8	von Margoldt (case 5): Ibid.	F	At birth	4 months	L	Electrical excision	Recovery	
9	Bidone: Arch. di ortop. **14**: 398, 1897	F	2 months	15 months	L	Extirpation	Recovery	
10	Kaufmann, reported by Usui (Arch. f. klin. Chir. **36**: 672, 1881): 40 Jahres. der Kinderspital, Basel, 1902	M	6 months	3 years	R	Extirpation	Facial palsy	Size of pigeon's egg
11	Harduin: Bull. et mém. Soc. anat. de Paris **79**: 714, 1904	F	1 month	5 months	R	Enucleation	Facial palsy	Little nevus on top of bluish tumor
12	Grulee: Surg. Gynec. Obst. **2**: 31, 1906	F	1 month	11 months	..	Operation	Cure	Two small nevi; skin bluish over deep tumor
13	Clogg (?): Report of the Society for the Study of Diseases of Children, 1906, vol. 6, p. 250	..	3 months	7 months	R	Operation	.....	Thought to be a vascular sarcoma
14	Biagi: Arch. di ortop. **24**: 257, 1907	F	1 month	2 months	..	Operation	Recovery	Size of hen's egg
15	Herxheimer: Centralbl. f. allg. Path. u. path. Anat. **19**: 709, 1908	M	.....	18 months	..	Enucleation		
16	Herxheimer: Ibid.	M	.....	18 months				
17	Levitt: Berl. klin. Wchnschr. **45**: 258, 1908	M	.....	18 months	R	Enucleation	Recovery	Size of child's fist
18	Levitt: Ibid.	F	2 months	3 months	L	Enucleation	Recovery	Plum sized
19	Hagendorn, mentioned by Usui (Vrach., 1908, no. 29), who examined the section, but did not include the case							
20	Ittmann: Inaugural Dissertation, München, 1909	F	2 months	18 months	L	Extirpation	Recovery	Plum sized
21	Rossi: Riv. di clin. pediat. **29**: 1007, 1909	F	1 month	8 months	..	Extirpation	Recovery	
22	Sangiorgi: Clin. chir. **17**: 1333, 1909	F	At brith	7 months	L	Removal	Recovery	Looked like hypertrophied parotid gland; skin bluish
23	von Haberer: Arch. f. klin. Chir. **93**: 817, 1910	F	At birth	4 months	R	Enucleation	Facial palsy	Size of hen's egg
24	Harrass and Suchier: Deutsche med. Wchnschr. **37**: 499, 1911	M	8 weeks	8 weeks	L			
25	Usui: Arch. f. klin. Chir. **94**: 1083, 1911	F	1 month	8 months	R	Extirpation	Recovery	Size of silver dollar; bluish skin
26	Usui: Ibid.	M	2 weeks	4 weeks	L	Extirpation	Facial palsy	Walnut size
27	Gellé and Petit-Dutaille: Bull. et mém. Soc. anat. de Paris **88**: 185, 1913	..	At birth	10 months	..	Operation	Recovery	Size of fist
28	Trinci: Riv. di clin. pediat. **13**: 541, 1915	..	.....	11 months	R	Extirpation	Recovery	
29	Trinci: Ibid.	..	3 months	10 months	R	Extirpation	Recovery	
30	Trinci: Ibid.	..	2 months	8 months	L	Extirpation	Recovery	Size of hen's egg

31	Trinci: Ibid.	..	Red dot at birth	4 weeks	L	Extirpation	Recovery	Size of pigeon's egg
32	Trinci: Ibid.	..	4 months	11 months	R	Extirpation	Recovery	
33	McFarland	M	At birth	5 months	L	Extirpation	Recovery	6 by 6 by 3 cm.

Submaxillary Glands

1	Kermission: Precis de Chirurgie Infantile, 1911							
2	Boekel: Nouveau Dictionaire de Chirurgie Practique, 1870, article "Erectile"							
3	Magnac: Bull. et mém. Soc. anat. de Paris **95**: 197, 1925	F	At birth	4 years	R	Extirpation	Recovery	Size of orange

Cavernous Angiomas of the Parotid Gland

1	Pilcher: Ann. Anat. & Surg. Soc. Brooklyn **2**: 111, 1880	F	At birth	.....	L	Removal	Facial palsy	
2	Notta: Bull. et mém. Soc. de chir. de Paris, 1880; cited by Tilleaux: Traite d'anatomie topographique, 1895, p. 277	F	47 years	4 years	R	Removal	Recovery	Called a cystic tumor
3	von Margoldt (case 2): Jahrb. f. Nat. u. Heilk. **6**: 250, 1897	F	At birth	9 months	L	Paquelin cautery	Death	Angioma of skin invading parotid gland
4	von Margoldt (case 3): Ibid.	M	At birth	7 months	L	Paquelin cautery	Not cured	Skin angioma excised; parotid paquelin
5	von Margoldt (case 4): Ibid.	F	At birth	11 months	L	No treatment		Cavernous angioma of skin and parotid
6	Conforti: Clin. chir., 1906, vol. 14 (reference not available)							
7	Routier: Bull. et mém. Soc. anat. de Paris **34**: 1189, 1908	M	.....	.....	..	Removal	Recurrence	The whole parotid region was pulsatile

Angiomas in the Parotid Region that May or May not Have Affected the Gland

1	Duke: Prov. Med. & Surg. J. **3**: 406, 1842; Gaz. d. hop., 2d series **4**: 276, 1842	..	3 months	9 months	..	.....	.....	Thought to be an aneurysm but a hypertrophied parotid gland
2	Boekel: no reference. Hartman (case 6): Rev. de chir. **9**: 756, 1889	F	.....	12 months		Destruction by setons		Large angioma of neck
3	Gascoyne: Tr. Path. Soc. London, 1860	M	.....	44 years	..	.....	Death	Had multiple angiomas
4	Guelliot: Bull. Soc. de méd. de Reims **4**: 250, 1898	F	.....	7 years	R	Removal	Facial palsy; recovery	Size of large nut
5	Folly: Union méd. et scient. du Nordest. **33**: 13, 1909	M	21 years	21 years	R			
6	Tuffier: Bull. et mém. Soc. de chir. de Paris **31**: 349, 1906	F	.....	2½ years	..	Infection and electrolysis	Cure	No further details
7	Abbe: Ann. Surg. **54**: 237, 1911	F	.....	.....	..	Radium irradiation	Disappearance in 4 weeks	
8	Rocher and Souchet: J. de méd. de Bordeaux **44**: 458, 1914	F	3 weeks	4 months	..	Electrolysis	.....	No details
9	Bianchini: Ann. ital. di chir. **4**: 607, 1925	F	7 years	27 years	..	.....	.....	Caused deformity of angle of jaw

Angiomas of the Skin of the Parotid Region not Known to Have Affected the Gland

1	Teale: Brit. M. J. **1**: 303, 1867	F	.....	4 months	..	Operation	Recovery	
2	Teale: Ibid.	F	.....	7 months	..	Operation	Recovery	
3	Teale: Ibid.	F	.....	5 months	..	Operation	Death	
4	Augier: Gaz. d. mal. infant. **9**: 25, 1907	..	At birth	7 months	L	Operation	(Adherent to skin)	Parotid gland not definitely invaded

Pulsating Vascular Lesion and Hematoma Following Traumatism

1	Polyna: Centralbl. f. Chir. **45**: 525, 1918	M	.....	.....	..	.....	.....	Followed a war injury

COMMENT

These tumors are benign, but if they are neglected, the vessels progressively increase in size, so that surgical removal becomes more difficult, and the operation is apt to be bloody. Removal of the entire affected gland seems to be the operation of election and has been followed by complete recovery (so far as the case reports show) in twenty-two of thirty-three cases. Care must be taken, however, lest the facial nerve be destroyed. Facial palsy has been reported in five cases.

The tumors occur with about equal frequency on the two sides of the face; right, twelve; left, thirteen. They are, however, notably more common in girls (fifteen) than in boys (eight). The tumors are usually noticed immediately after birth, though in one reported case the tumor is said not to have been detected until the sixth month. In two of the cases reported with the necessary data, the patient escaped operation until 3 years of age. The youngest patient to be operated on was only 4 weeks old. The average age at which operation was performed was 9 months.

The size of the tumors removed by operation varied from the size of a pigeon's egg to that of a fist. But regardless of size they must have been of much the same general appearance, as it is frequently stated that they looked like hypertrophied parotid glands.

The authors of previous contributions on the subject differed among themselves as to the number of reported cases and the particular reported cases they were willing to admit to the first of the following groups. The conclusions reached by me and my classification of the cases are shown in the following tabulation and bibliography.

The literature on angioma of the salivary glands shows such tumors to be rare. A complete survey of the subject has resulted in the collection of reports of only fifty-seven cases roughly divisible as follows:

1. *Congenital Capillary Hemangioma of the Salivary Gland.*—The cases are all in infants or small children in whom the entire parotid (or submaxillary) gland, immediately after birth, began to enlarge for no apparent reason, until it attained to many times the normal size. In some cases, there was a small visible angioma in the skin or some purplish discoloration of the skin; in other cases, there was no gross indication of the nature of the lesion. Of such cases, including the one reported in this contribution, thirty-three are recorded as affecting the parotid gland, and three as affecting the submaxillary gland.

2. *Cavernous Angioma of the Salivary Gland.*—This group includes: seven cases in which a distinct superficial vascular nevus of the skin descended to and invaded the parotid, and nine cases in which a large, widely distributed hemangioma of the side of the face and neck invaded the parotid gland, as well as other adjacent structures.

3. *Vascular Nevi.*—These are hemangiomas of the skin over the parotid region which are not known to have invaded or trespassed on the parotid or submaxillary glands. Four cases are recorded.

4. *Pulsating Vascular Lesion.*—One such hematoma following traumatism is on record.

SUMMARY

A case of congenital capillary hemangioma of the parotid gland of an infant is described. Reports of thirty-three similar cases have been collected from the literature. The surgical removal of the entire affected gland is the operation of election and results in complete cure in most cases, though facial palsy has occurred in five cases. The tumor is benign. No case of recurrence is on record.

Other varieties of angiomatous disease of the parotid gland are introduced into the bibliographic tabulation for purposes of comparison.

THE EFFECT OF HEMOLYTIC TOXINS ON NERVOUS TISSUE *

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In a study of the effect of anemia on the spinal cord based on clinical and microscopic material, it had been concluded that anemia in itself does not produce the picture of subacute combined degeneration. It was only in the pernicious type of anemia that this degeneration of myelin sheath and axon was seen. Support was given to the theories of other investigators that one and the same toxin acted destructively on the hematopoietic system and the spinal cord, though the diseases might reveal themselves at different periods.[1]

As a result of this histologic research, the idea was conceived to investigate the effect of hemolytic agents on the myelin sheaths of nerve fibers of the spinal cord and peripheral nerves.

Frequently, the attempt has been made to produce degenerative processes of the central nervous system in animals by the injection of hemolytic agents. Experiments with the group of substances producing methemoglobin have been a complete failure. In experiments with the second group of hemolytic substances which act on the stroma or (hypothetical) pellicle of the red blood cells, the immense toxicity of these substances had been an obstacle to investigation. It was only recently that Rezek and Kollet [2] reported on a series of injections of saponin into a group of sixty rabbits, only two of which showed paralysis clinically. In the one case that was examined post mortem, degeneration of ganglion cells and demyelinization of nerve fibers were seen. But the authors did not conclude that this was the direct effect of saponin; they thought rather that the hypercholesteremia or the severe damage of the liver might have been responsible indirectly for the disease of the nervous system.

Attempts to produce demyelinization in the living animal by long extended ether or chloroform anesthesia did not meet with success.[3] In test tube experiments, it is possible to dissolve the myelin sheaths with lipoid solvents. After treatment with absolute alcohol for twenty-

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* From the Institute of Neurology, Northwestern University.

1. Weil, A., and Davison, Charles: Changes in the Spinal Cord in Anemia: A Clinicomicroscopic Study, Arch. Neurol. & Psychiat. **22**:966, 1929.

2. Rezek, P., and Kollet, V.: Virchows Arch. f. path. Anat. **270**:706, 1929.

3. Weil, A.: Arch. f. d. ges. Physiol. **223**:351, 1929.

four hours at 37 C., the myelin sheaths of spinal cords were partly dissolved, indistinct in their outlines. The axons in sections stained with Weil's method were unstained; glia fibers, distinctly stained. After treatment with pyridine for twenty-four hours at 37 C., the myelin sheaths of spinal cords were completely dissolved; the axons of the myelinated fibers stained dark black. It was not possible to obtain demyelinization with these solvents in formaldehyde-fixed tissue.

The plan of the present investigation was to study the effect of hemolytic toxins on nervous tissue in test tube experiments. This effect was to be compared with the effect of the same toxin on red blood cells, and the question was to be answered whether the basic principles governing hemolysis by those toxins could also be applied to myelolysis.

METHOD

Representatives of four different groups of hemolytic toxins were chosen for the present investigation: (1) saponin (Merck's purified bark of *Quillaja saponaria*); (2) cobra venom (dried saliva of *Naja nigricollis*, through the courtesy of Dr. T. Friedman); (3) sodium taurocholate (Merck's; about 42 per cent), and (4) streptolysin (strain of *Streptococcus haemolyticus*, through the courtesy of the Department of Bacteriology of Northwestern University; eighteen-hour meat-broth-serum cultures, centrifugated). In addition in control experiments, different substances that form methemoglobin in the animal body were tested together with the influence of different buffer solutions.

Cats and dogs were anesthetized with ether, killed by bleeding and the lower third of the cervical spinal cord or the sciatic nerves were removed under aseptic precautions. The spinal cord was cut into small segments of approximately 0.2 Gm. each, which were placed on a layer of cotton in sterilized test tubes. The solution of the substance to be investigated was added, and the tube closed by cotton and placed in the incubator. At the end of the experiment, the solution was replaced by a diluted solution of formaldehyde, U. S. P. (1:5), and the tissue was fixed for three days. It was then embedded in paraffin or a collodion preparation, and sections were stained by Weil's method for myelin sheaths or by a modified light-green fuchsin method. In some experiments, the whole formaldehyde-fixed tissue was impregnated according to the Bielschowsky method.

OBSERVATIONS

The Effect of Hemolytic Toxins on the Myelin Sheaths.—The four hemolytic toxins that were investigated produced hemolysis by dissolving the lipoid pellicles of the red blood cells.[4] In a similar way, they dissolved the myelin sheaths of myelinated nerve fibers. That saponin acted on the stroma (pellicle) of the red blood cells and not on the hemoglobin or the hypothetical hemoglobin-lipoid compound, as sug-

4. Landsteiner, K., in Oppenheimer, C.: Handbuch der Biochemie, Jena, A. Kanitz, 1910, vol. 2, p. 459. Blumenthal, G.: Ibid., 1925, vol. 3, p. 568. Von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, E. St. Faust, 1927, vol. 4, pt. 2, p. 1745.

gested by Lepeschkin [5] was demonstrated by experiment as follows: Red blood cells were hemolized with distilled water, centrifugated, washed and again centrifugated. The remaining stromata were spread on a glass slide and stained with one of the methods for myelin sheaths (Spielmeyer, Loyez, Weil). They assumed a black color similar to that of myelin sheaths. Another smear with stromata was left for ten minutes at 37 C. in a 1 per cent solution of saponin. After the staining only a pale gray color remained.

One per cent solutions of saponin, cobra venom and sodium taurocholate (2.4 per cent solution of Merck's 42 per cent preparation), as well as eighteen-hour cultures of *Streptococcus haemolyticus* kept twenty-four hours at 37 C., produced a definite demyelinization. In transverse sections of spinal cords or sciatic nerves stained for myelin sheaths, a pale, unstained zone could be seen encircling the spinal cord or forming the outer zone of the transversely cut nerve trunks. If solutions of 1 per cent or stronger of saponin were applied for twenty hours, under the microscope, a loose meshwork of faintly stained axons and glia fibers was seen, intermingled with the fibers of the connective tissue frame work (fig. 1, *A*, *B*, *C* and *D*). The glia nuclei were well stained. In the transitional zone toward the nonaffected tissue, single myelin sheaths were left partly interrupted and thinned out (fig. 2, *B* and *D*). There was a definite difference in comparison with the controls kept in 0.9 per cent sodium chloride solution, Fleisch's solution or Ringer's solution. The myelin sheaths here were swollen and distorted, but they had not lost their staining qualities, and there was never a zone of demyelinization as regular in outline as in the first group of experiments (fig. 2, *A* and *C*). In the controls, the axons, too, were swollen, though stainable with Bielschowsky's method. In the experiments with the hemolytic toxins, the axons appeared to be thinner and more lightly stained than in normal material or in the controls. The astrocytes and their fibers were well stained in Cajal's gold-mercuric chloride preparations of spinal cords. The zone of demyelinization could be extended at will into the spinal cord or into the peripheral nerves by artificial lesions or longitudinal sectioning.

The Quantitative Effect of Hemolytic Toxins on the Myelin Sheaths.—The amount of red blood cells dissolved by saponin was not proportional to the amount of saponin used, but increased disproportionally with rising concentrations. The same condition applied to the dissolution of the myelin sheath. The effect of a 2 per cent solution of saponin seemed to be more intensive than twice the effect of a 1 per cent solution. Under the microscope, the destruction of nervous tissue seemed to be more intensive after the use of a 2 per cent solution,

5. Lepeschkin, W. W.: Abstracts of communications to the XIIIth Internat. Physiol. Congress, Boston, 1929.

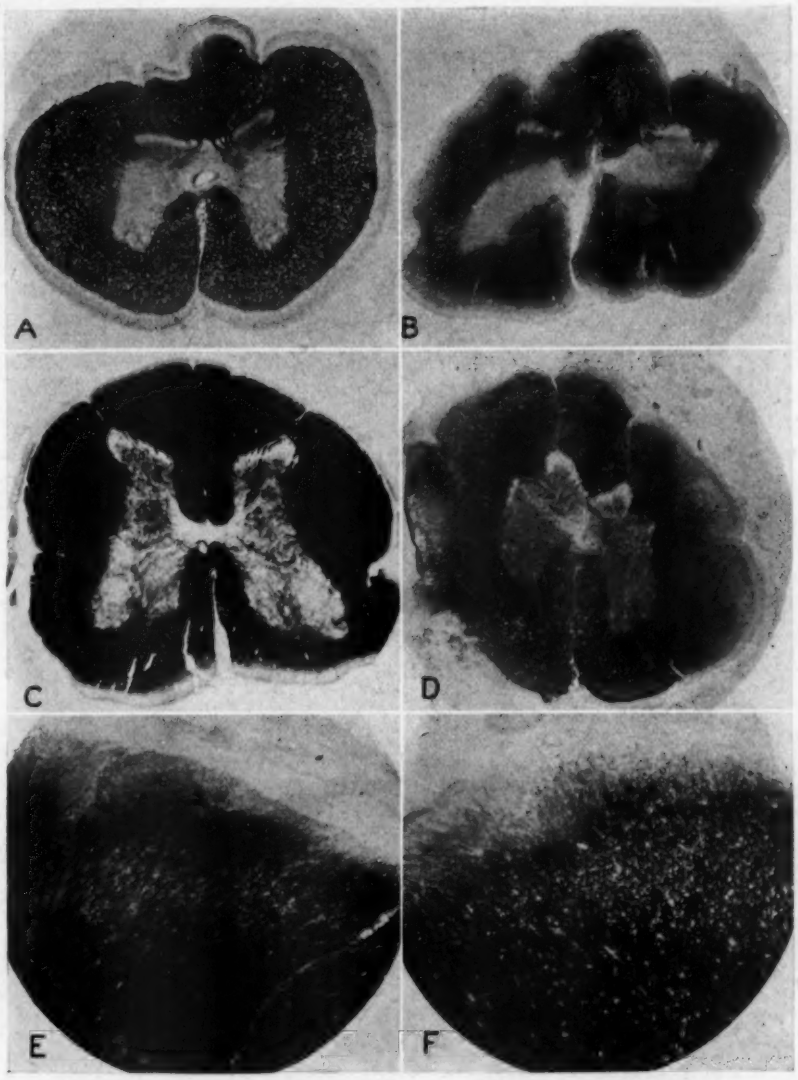

Fig. 1.—*A*, spinal cord of cat after incubation with 2 per cent saponin in Fleisch's solution, forty-eight hours at 37 C. A transverse section of spinal cord is shown, stained by Weil's method, and seen by Leitz objective 3.2, ocular 3 ×. The purpose is to demonstrate the peripheral zone of demyelinization. *B*, spinal cord of dog after incubation with a 1 per cent solution of sodium taurocholate in 0.9 per cent NaCl twenty-four hours at 37 C. The technic of staining in *B*, *C* and *D* is the same as in *A*. *C*, spinal cord of dog after incubation with a 0.5 per cent solution of cobra venom in 0.9 per cent NaCl twenty-four hours at 37 C. Note the demyelinization of the posterior roots. *D*, spinal cord of cat after incubation for twenty-four hours at 37 C. with 50 cc. of meat-broth-serum culture of Streptococcus haemolyticus eighteen hours old. *E*, spinal cord of dog (0.150 Gm.) in an emulsion of 0.6 Gm. of saponin-lecithin 1 : 5 in 10 cc. 0.9 per cent NaCl. A transverse section is shown, stained by Weil's method and seen by Leitz objective 3.2, ocular 6 ×. The purpose is to demonstrate the diminished demyelinization as compared with the action of saponin-lecithin 1 : 1 in *F*. *F*, spinal cord of dog (0.145 Gm.) in an emulsion of 0.2 Gm. of saponin-lecithin 1 : 1 in 10 cc. of 0.9 per cent sodium chloride. The technic and the enlargement are the same as in *E*. The purpose is to demonstrate the marginal zone of demyelinization.

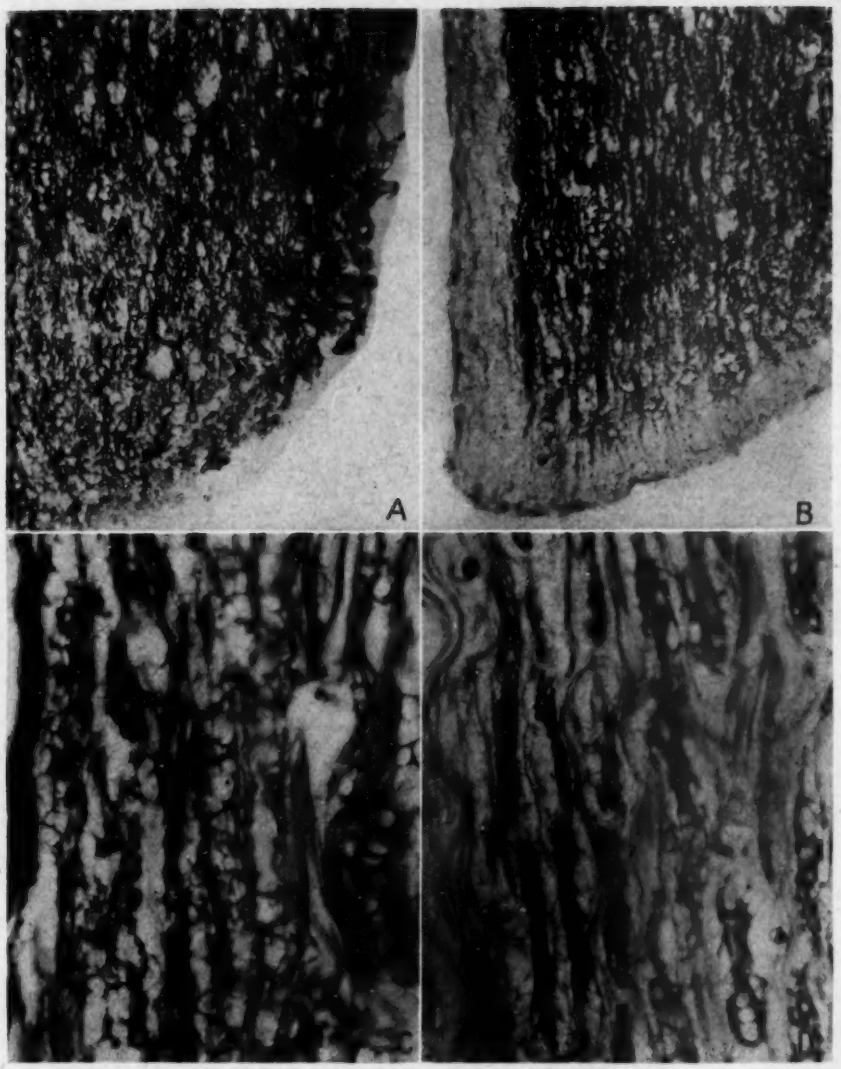

Fig. 2.—*A*, spinal cord of cat in Fleisch's solution seventy-two hours at 37 C. Longitudinal section is shown, stained by Weil's method and seen by Leitz objective 10, ocular 8 ×. A control to demonstrate that seventy-two hours of autolysis did not change the staining qualities and did not produce the marginal zone of demyelinization. *B*, spinal cord of cat after incubation with 0.5 per cent saponin in Fleisch's solution for twenty-four hours at 37 C. A longitudinal section is shown, stained by Weil's method. The enlargement is the same as in *A*. The purpose is to demonstrate the marginal zone of demyelinization at the outer wall and at the cut surface. *C*, sciatic nerve of dog in 0.9 per cent solution of NaCl for twenty-four hours at 37 C. A longitudinal section is shown, stained with light green-fuchsin and seen with Leitz objective 2 mm., ocular 6 ×. The purpose is to demonstrate the absence of myelin sheath dissolution in the controls. *D*, sciatic nerve of dog in 1 per cent solution of saponin in 0.9 per cent NaCl for twenty-four hours at 37 C. A longitudinal section is shown, stained and enlarged as in *C*. The purpose is to demonstrate the dissolution of myelin sheaths.

though the zone of demyelinization was not exactly twice as wide as after the application of a 1 per cent solution.

In order to determine objectively the amount of saponin which was bound by spinal cords, solutions of the toxin were tested for their hemolytic power at the beginning and the end of the experiment. After incubation at 37 C. for forty-eight hours, 1 cc. of the solution was diluted with 9 cc. of 0.9 per cent sodium chloride; 1 cc. of this dilution was added to 1 cc. of a 2.5 per cent emulsion of red blood cells which

TABLE 1.—*Comparison of Action of Saponin Against Spinal Cords of Cats and Dogs After Forty-Eight Hours' Incubation*

Animal	Mg. Spinal Cord	Mg. Saponin in 1% Solution	1 Cc. 0.1% Dilution Equivalent to 0.1% Saponin, Cc.	Saponin Absorbed, Mg.	Mg. Saponin per 1 Gm. Spinal Cord	Final Concentration, %
Cat	215	75	0.40	45	209	0.40
Cat	529	100	0.30	70	135	0.30
Dog	210	75	0.43	43	205	0.43
Dog	510	100	0.21	79	158	0.21
Control	...	50	1.00	..	...	1.00

TABLE 2.—*Results of Experiments with a 1 per Cent Solution of Saponin and Dog Spinal Cord, Incubated Forty-Eight Hours at 37 C.*

Mg. Saponin per 1 Gm. of Spinal Cord	Absorbed Mg. Saponin per 1 Gm. Spinal Cord	Final Concentration of Saponin, %	Constant of Arrhenius' Formula*	
64	63	0.01	1,357	
81	78	0.03	809	
100	95	0.06	620	
115	114	0.05	840	
134	116	0.13	901	
200	156	0.21	447	
245	177	0.28	414	
300	200	0.29	489	
348	209	0.40	386	
440	240	0.45	409	
222	201	0.21	569	spinal cord
345	240	0.30	536	emulsions

* For explanation, see under "The Physicochemical Nature of the Process of Demyelinization."

had been washed with salt solution. The time for complete hemolysis was determined. At the same time, varying amounts of a 0.1 per cent solution of saponin filled up to 1 cc. with 0.9 per cent sodium chloride were added to 1 cc. of the blood emulsion, and the time for complete hemolysis was determined.

To give an example of these experiments, a protocol is shown in table 1. It illustrates an experiment which was to answer the question whether spinal cords of cats and dogs acted quantitatively differently against saponin.

Table 2 gives the results of experiments carried out in order to determine the amount of saponin which was bound by 1 Gm. of spinal cord in solutions of different concentrations.

Most of these experiments were carried out with sections of spinal cords in which the possible retarding influence of the diffusion of the solution into the tissue had been balanced by extending the time to forty-eight hours. The inhibiting influence of saponin on autolysis and fermentative processes makes such an extension possible. When an emulsion of spinal cord was used, prepared by grinding the tissue with the solution in a mortar, approximately 20 per cent more saponin was bound than by the intact tissue.

Influence of Time; Minimal Concentration.—Twenty-five hundredths of a milligram of saponin in 0.1 per cent solution completely hemolysed 1 cc. of a 2.5 per cent emulsion of blood cells if kept for several hours in the incubator at 37 C.; 0.15 mg. of saponin can no longer produce complete hemolysis under the same conditions. In similar investigations of saponin myelolysis, the first effect of a 1 per cent solution could be detected under the microscope after approximately one hour. The

TABLE 3.—*Comparison of Hemolytic, Myelolytic and Toxic Effects*

	Saponin	Cobra Venom	Sodium Taurocholate	Strepto-lysin*
Hemolytic effect	100	30	150	20
Myelolytic effect	100	150	200	200
Toxic effect	100	15,000	30	...

* 0.2 Gm. of spinal cord of dog in 50 cc. of an eighteen-hour culture.

maximal effect, measured by the width of the zone of demyelinization, was practically obtained after twenty hours. A 0.5 per cent solution produced only a minimal effect; a 0.2 per cent solution was ineffective after twenty-four hours' incubation. Controls with serum of dogs and cats, plasma of the same animals and of rabbits, meat-broth, meat-broth-serum, saliva, phenylhydrazine, acetanilid, potassium chlorate and oil of sesame did not show demyelinization.

Comparison of the Hemolytic, the Myelolytic and the Toxic Effects.—The comparative hemolytic effects of the different toxins were determined by investigating the amount of saponin which was necessary to produce complete hemolysis of 1 cc. of an emulsion of red blood cells within the same time as a given amount of each of the other three toxins in equal dilutions. The myelolytic effects were compared by measuring with an ocular micrometer at an enlargement of 600 times the average width of the zone of demyelinization in microns in transverse sections of spinal cords. Approximately the same amount of spinal cord and the same dilution of toxin were used in all experiments of this series. The effect of a 0.1 per cent solution of saponin was taken as a unit in testing the hemolytic effect and that of a 1 per cent

solution of saponin was used as a standard in comparing the myelolytic effects. The toxic effects were determined arbitrarily by comparing the lengths of time that it took the various toxins to kill white rats of similar weight after intra-abdominal injection, the same amount of toxin being used in each instance.

The Neutralizing Effect of Lipoids on the Hemolytic, Myelolytic and Toxic Action of Saponin.—It has long been known that cholesterol and lecithin added to saponin reduce its hemolytic power. The same is true for a combination of lecithin and streptococcus hemolysin (Gordon and Stansfield [6]). Small amounts of lecithin added to saponin do not have this effect, while large amounts inhibit hemolysis (Kobert [7]). In order to find out whether the myelolytic and toxic effects of saponin

TABLE 4.—*The Toxicity of Different Saponin-Lipid Combinations as Indicated by the Time Each Took to Kill After Intra-Abdominal Injection*

Combination Injected	Rat Weight, Gm.	Mg. Substance	Mg. Saponin per 100 Gm. Weight	Minutes Before Death	Evaluation of Toxic Effect
Saponin	182	36	20	123	100
Saponin-lecithin 1:1	174	70	20	172	72
Saponin-lecithin 1:5	168	205	20	253	49
Saponin	123	37	30	112	100
Saponin-lecithin 1:1	120	72	30	106	105
Saponin-lecithin 1:5	120	220	30	227	47
Saponin	145	29	20	132	100
Saponin-galactolipids 1:1	130	52	20	109	121
Saponin-galactolipids 1:5	130	155	20	208	64
Saponin	146	44	30	122	100
Saponin-galactolipids 1:1	129	78	30	119	102
Saponin-galactolipids 1:5	142	255	30	122	100

are influenced in the same way by combinations with lipoids, as is the hemolytic effect, experiments were carried out as follows:

Following Kobert's example, recrystallized cholesterol and different raw lipids, as well as purified lecithin, obtained with MacLean's method from dogs' brains and spinal cords, were added to saponin, and the mixtures were boiled with absolute alcohol (100 parts) in the reflux condenser for thirty minutes. The alcohol was evaporated, and the remaining substance was taken up with chloroform. It was found that the mixture of saponin with lecithin, cephalin or galactolipids completely changed its physical properties. The remaining mixtures were easily soluble in chloroform and gave emulsions with water. The combinations with cholesterol and sphingomyelin were not as successful. After treatment with chloroform, approximately 75 per cent of the original saponin remained insoluble. Further experiments are necessary to prove whether an extended time of boiling gives better results. The different combinations which were obtained were tested for hemolysis, myelolysis and toxicity in the same way as was described for the four toxins in the preceding paragraph (fig. 1, *E* and *F*).

6. Gordon, J., and Stansfield, F. R.: Brit. J. Exper. Path. **10**:191, 1929.

7. Kobert, R.: Beitraege zur Kenntnis der Saponinsubstanzen, Stuttgart. Ferdinand Enke, 1904.

In order to give an illustration of the toxic effect of saponin and its different lipid combinations, some protocols are copied in table 4. Two different combinations with lecithin and galactolipids were tested: one in which one part of saponin had been combined with one part of the lipid and a second in which one part of saponin had been combined with five parts of the lipid. In table 5, the experiments with 30 mg. saponin per hundred grams of weight are selected for comparative purposes.

The inhibitory effect of lecithin on sodium taurocholate was much more pronounced. Five parts of egg-lecithin completely neutralized the toxic and myelolytic effect of one part of the toxin.

The Neutralizing Action of Brain Emulsion and Red Blood Cells on the Hemolytic, Myelolytic and Toxic Effects of Saponin.—The experiments of Flexner and Noguchi [8] demonstrated that brain emulsion added to cobra venom reduces its toxic effect, while red blood cells added to the toxin do not influence its toxicity. Similar experiments were

TABLE 5.—*Comparison of the Hemolytic, Myelolytic and Toxic Effects of Saponin-Lipid Combinations*

	Saponin	Saponin-Lecithin 1:1	Saponin-Lecithin 1:5	Saponin-Galactolipids 1:1	Saponin-Galactolipids 1:5
Hemolytic effect	100	100	Trace	100	Trace
Myelolytic effect	100	110	30	100	100
Toxic effect	100	105	47	102	100

carried out with saponin. Dogs' erythrocytes to the amount of 7.5 cc., washed twice with 0.9 per cent sodium chloride solution were mixed with 1.5 cc. of a 2 per cent solution of saponin. The mixture was incubated for two hours at 37 C. and then centrifugated. A residue of intact red blood cells remained. The supernatant fluid added to a fresh blood cell emulsion (0.5 cc. to 1 cc. of a 2.5 per cent blood emulsion with 0.5 cc. of 0.9 per cent sodium chloride) did not produce hemolysis within two hours, while 1 cc. of a 0.1 per cent solution of saponin produced complete hemolysis immediately.

The mixture of red blood cells and saponin (7.25 cc.) was injected intra-abdominally into a white rat of 100 Gm. weight, which died after 273 minutes. The injection of a corresponding amount of saponin in 2 per cent solution (1.5 cc.) into the control, i.e., 30 mg. of saponin per hundred grams of weight, killed the control after 102 minutes.

Two grams of gray matter and 2 Gm. of white matter from a dog's brain were each emulsified with 3 cc. of a 2 per cent solution of saponin, and the mixtures were incubated for two hours at 37 C. Hemolysis could no longer be produced by the mixture of saponin and white matter with ten times the amount of the minimal hemolytic dose

8. Flexner, S., and Noguchi, H.: J. Exper. Med. **6**:279, 1902.

of saponin. The mixture of saponin and gray matter had not completely lost its hemolytic effect, although, expressed in saponin units, it was only $\frac{1}{10}$. These mixtures injected into white rats in amounts corresponding to 30 mg. of saponin per hundred grams of weight were much less toxic than saponin. After six hours, both the animal into which the emulsion of gray matter and saponin had been injected and that into which the emulsion of white matter and saponin had been injected were still alive.

In another series of experiments, the whole brain substance was emulsified with saponin. After two hours' incubation at 37 C., the mixture was centrifugated, and the supernatant fluid was injected into rats. As in the preceding experiments, the animals were still alive after six hours, while the controls, into which saponin only had been injected, died within two hours. The demyelinization of spinal cords in test tube experiments was influenced in the same way as the toxic effect. The spinal cord which had been incubated with the mixture of saponin and red blood cells showed only a small peripheral zone of demyelinization with greater damage to the posterior roots. The spinal cord, which had been incubated with the supernatant fluid of the centrifugated mixture of saponin and brain substance, presented only a trace of demyelinization in the outer zone. A similar protecting influence against the action of saponin was noticed in controls in which spinal cord was incubated with mixtures of saponin and dog serum.

The Physicochemical Nature of the Process of Demyelinization.— The question arises as to whether the dissolution of the myelin sheaths by the hemolytic toxins which were investigated follows the same physicochemical laws that govern the hemolysis of red blood cells. In studying sections of spinal cords and nerves that have been under the influence of saponin, one is under the impression that the sheaths are dissolved or melted away as a structure of ice melts when heated. The longitudinal sections in figure 2 *B* and *D* represent this thinning out and gradual disappearance of the myelin sheaths in the transitional zones. Spinal cords treated with sodium taurochorlate differ histologically somewhat from those treated with the three other toxins. One sees numerous black globules in sections stained by Weil's method. The globules in the outer zones are smaller and less numerous than those in the transitional zone.

The hemolytic action of these toxins has been generally ascribed to the dissolution or destruction of the lipoids of the stroma (pellicle) of the red blood cells. It was assumed either that the toxin combines directly with the lipoids, as in the case of saponin (Kobert), or that, as in the instance of cobra venom, in lipids (lecithin and cephalin) the radical of the unsaturated fatty acid was split off and the remaining

rest (lysolecithin and lysocephalin) acted as a toxin (Kyes; Luedecke; Delezenne and Ledebt; Levene and Rolf, and others[9]).

The effect of saponin on the lipids of the spinal cord can be controlled by analyses for phosphorus. If one carries out a fractional extraction of spinal cord by MacLean's method, one finds that after treatment with solutions of saponin approximately 25 per cent of the total phosphorus has been transferred into the solution. In experiments with brain substance, this amount is approximately 47 per cent. Although saponin applied in concentrated solutions (3 per cent) inhibits autolysis, it is not possible to decide whether or not the increase of phosphorus in water soluble form is due only to the emulsifying effect of the saponin. Experiments with nervous tissue in which fermentative processes have been inhibited by heating or otherwise may give a better answer to this question.

TABLE 6.—*Distribution of Phosphorus After Fractionate Extraction of Nervous Tissues*

	Percentage of Total Phosphorus					
	Brain			Spinal Cord		
	Normal	Saponin*	Autolysis†	Normal	Saponin*	Autolysis†
Water solution	....	47.0	76.0	....	25.0	62.6
Acetone extract	16.3	9.7	9.5	7.3	17.6	15.0
Alcohol extract	54.7	31.5	6.7	77.2	47.0	19.3
Residue	29.0	11.8	7.8	15.5	10.4	3.1

* Dogs' brains and spinal cords used, with 10 cc. of 3 per cent solution of saponin per 1 Gm. of substance.

† For the experiments with autolysis, 10 cc. of 0.9 per cent sodium chloride was used per 1 Gm. of substance. The mixtures were kept for forty-eight hours at 37 C.

Table 6 reports the results of fractional extractions of normal nervous tissue, brain and spinal cord after treatment with saponin and after autolysis.

The amount of red blood cells dissolved by saponin is not proportional to the amount of saponin used, but increases disproportionately with rising concentrations. The same is true for the binding of hemolytic amboceptors and for the binding of saponin to the spinal cord as demonstrated in table 2. Arrhenius[10] believed that the binding of the hemolytic amboceptor to red blood cells could be quantitatively expressed by the formula $B=K\,C^n$. B is the amount of the absorbed amboceptor, C is the concentration of the system at the end of the experiment, K and n are constants ($n=\frac{2}{3}$ in the experiments of Arrhenius). If one calculates K for the absorption of saponin by spinal cord in table 2, one finds that the values for K are surprisingly constant if one comes to

9. Literature in Delezenne, C., and Fourneau, E.: Bull. Soc. chim. biol. **15**: 421, 1914. Levene, P. A., and Rolf, J. P.: J. Biol. Chem. **55**:743, 1923.

10. Arrhenius, S.: Immunochemie, Ergebn. d. Physiol. **7**:480, 1908.

final concentrations which are still strong enough to produce myelolysis, i.e., concentrations of more than 0.2 per cent.

Arrhenius concluded from his experiments that the distribution of the hemolytic amboceptor between red blood cells and the serum followed the law of distribution of a substance between two solvents. Blumenthal [4] opposed this view. In quoting the literature on this subject, he summarized the different theories which try to explain the phenomenon of hemolysis. The present tendency seems to be to explain it by comparing the binding of the hemolytic amboceptor to the red blood cells with the adsorption of colloids.

It may be sufficient for the purpose of this paper to point out the constancy of K in the application of Arrhenius' formula to the binding of saponin to spinal cord.

TABLE 7.—*Lipoid Content of Red Blood Cells and of Nervous Tissue*

	Dog				Cat		
		Brain†					
Lipoid	100 Cc. Erythrocytes*	Gray Matter	White Matter	Spinal Cord†	100 Cc. Erythrocytes*	Brain†	Spinal Cord†
Cholesterol.....	0.215	2.81	3.94	5.31	0.232	2.48	5.57
Lecithin.....	0.245	0.87	1.96	2.38	0.310	1.19	2.58
Total lipoids‡.....	0.562-0.634	10.60	19.60	24.20	0.531-0.589	13.80	23.40

* The figures for cholesterol of red blood cells are from the publications of Knud and Iwatsuru, those for lecithin of red blood cells from Abderhalden (quoted in Oppenheimer, footnote 4, p. 569).

† The figures for nervous tissue were copied from Weil (J. Biol. Chem. **83**: 601, 1929). The latter figures are for percentages of fresh tissue.

‡ The total lipoids of the red blood cells were calculated as triolein. The numbers for the total lipoids of the nervous tissues represent the total amount of lipoids after extraction by acetone and following alcohol extraction in the Soxhlet apparatus.

The results of the experiments to combine saponin with varying amounts of lipids demonstrated the ability of the toxin to form emulsions with large amounts of the substance to become emulsified. It could be shown that with increasing amounts of lipids added, the hemolytic power, in test tube experiments, became gradually diminished. It seemed that galactolipids did not act in the same direction as lecithin. The combination of saponin-lecithin 1 : 5 was much less hemolytic, myelolytic and toxic than the combination 1 : 1. In the combinations with galactolipids, however, it did not make any difference whether one or five parts were added to one part of saponin (tables 4 and 5). It should be noted that myelolytic and toxic effects were affected in the same manner.

In order to obtain a basis for the explanation of the different binding powers of red blood cells and of nervous tissue for saponin by their different lipoid contents, the figures in table 7 are cited.

These figures indicate that 1 Gm. of spinal cord contains 242 mg. total lipoids (dog) or 234 mg. (cat); and that 1 cc. of red blood cells

contains 6 mg. total lipoids (dog) or 5.6 mg. (cat). The optimal amount of saponin which may be bound by 1 Gm. of spinal cord is 240 mg. The minimal amount of saponin which is sufficient to produce complete hemolysis of 1 cc. of red blood cells is approximately 5 mg. (0.25 cc. of 0.1 per cent saponin for 1 cc. of 5 per cent red blood cells). If one combines these different facts, one finds that in hemolysis, as well as in the process of myelolysis, one part of Merck's saponin is bound by approximately one part of total lipoids.

The Identity of Hemolysins, Myelolysins and Neurotoxins.—The classic experiments of Ehrlich [11] in demonstrating the different action of the hemolytic (tetanolysin) and the toxic (tetanospasmin) principles in the tetanus toxin belong to the fundamentals of the side (lateral)-chain theory. If one adds erythrocytes to tetanus toxin, it loses its hemolytic power, in test tube experiments ("the tetanolysin is bound"), while this mixture still produces tetanus after injection into an animal ("the tetanospasmin remains free"). A similar experiment to demonstrate the difference between the hemolytic and the neurotoxic principles in cobra venom was carried out by Flexner and Noguchi.[8] Cobra venom mixed with brain emulsion was still hemolytic, but much less toxic, while a mixture of blood cells and venom was very toxic. They concluded that their experiments supported the hypothetical considerations of the lateral chain theory of immunity, i.e., that brain cells contain the receptors for the neurotoxic constituent of the venom, while red blood cells furnish the receptors for the hemolytic principle.

If one replaces the words "tetanustoxin" and "cobra venom" by the word "saponin," the statement of the results of the experiments would read as follows: 1. If one adds erythrocytes to saponin, it loses its hemolytic power, while the mixture still produces death after injection into an animal. 2. Saponin mixed with brain emulsion is still hemolytic but less toxic, while a mixture of red blood cells and saponin is very toxic. These facts have been fulfilled experimentally, as was demonstrated in the protocols under "Comparison of the Hemolytic, the Myelolytic and the Toxic Effects."

In these experiments and in the experiments with saponin-lipid combinations, the chemically unknown animal and bacterial toxins had been replaced by a chemically relatively well known substance. The active principle of Quillaja saponin has been isolated in the form of sapotoxin (Brandl [12]). It is a chemically uniform substance which dissolves red blood cells, which produces local inflammation after subcutaneous injection and which injected in larger amounts produces death. One may assume that its action on the myelin sheath is the same as that of saponin,

11. Ehrlich, P.: Berl. klin. Wchnschr. **35**:273, 1898.

12. Brandl, J.: Arch. f. exper. Path. u. Pharmakol. **54**:245, 1904.

its mother substance. In other words, the hemolytic, myelolytic and toxic principles in saponin are represented by one and the same chemical unit. Furthermore, these different effects on red blood cells and the nervous tissues may be influenced in the same way by lipoids, by red blood cells and by brain emulsions as the hemolytic and toxic effects of bacterial and animal toxins. One is able at will to reduce the hemolytic action without impairing the myelolytic and toxic effect of saponin. Taking all these different facts together, one seems justified in establishing the following hypothesis for further research:

The effects of bacterial and animal toxins which at the same time act in a hemolytic, myelolytic and toxic manner are not reproduced by different principles but by one and the same toxic substance. Its physiologic action is determined by the lipoid content of the tissue on which this toxin is acting and by the lipoid content of the solvent of the toxin. Combinations of these toxins with the lipoids of red blood cells, in test tube experiments, may be split up again after contact with the living tissues, and the neurotoxic effect may reveal itself, though delayed. Combinations of these toxins with brain emulsions undergo the same action after injection into an animal. In test tube experiments with erythrocytes, their adsorption to the lipoids of the nervous tissues prevents a competitive adsorption to the lipoids of the red blood cells.

The Relation of Myelolysis by Toxins to Neurologic Diseases.—The classic examples of primary myelin sheath degeneration in man are multiple sclerosis and subacute combined degeneration in pernicious anemia. It is tempting to try to explain the histologic pictures of demyelination by the action of a toxin which might be related to the group of hemolytic toxins which were investigated. But besides proving that such a toxin is present in these diseases, it has to be demonstrated how such a toxin circulating in the blood and in the lymphatic fluids can penetrate into the central nervous system. That this barrier of blood and cerebrospinal fluid (Blut- Liquorschranke) may be penetrated under certain conditions in disease has been well demonstrated by the investigations of Walter and others.[13] It is known that hemolysins are found in the cerebrospinal fluid in syphilitic disease (Weil and Kafka).[14] Singer and Muenzer [15] demonstrated hemolytic amboceptors in the spinal fluid of patients suffering from general paresis and chronic epidemic encephalitis six days after the injection of sheep blood intravenously. Histologic pictures of marginal demyelinization of the spinal cord resembling the figures that are produced in this paper have been

13. Walter, F. K.: Arch. f. Psychiat. **79**:363, 1927. Weil, E.: Ztschr. f. d. ges. Neurol. u. Psychiat. **24**:507, 1914.

14. Weil, E., and Kafka, V.: Med. Klin. **7**:1314, 1911.

15. Singer, E., and Muenzer, T.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:532, 1926.

described by Spitzer [16] as occurring in tabes dorsalis and by Martin [17] as occurring in amyotrophic syphilitic meningomyelitis. Of interest in connection with the problems presented is the report of Laignel-Lavastine and Koressios [18] that they succeeded in improving the conditions of patients suffering from multiple sclerosis by the injection of hemolytic rabbit serum (against sheep blood).

CONCLUSIONS

The hemolytic and myelolytic actions of saponin, sodium taurocholate, cobra venom and streptolysin were studied. It could be demonstrated that hemolytic toxins dissolve the myelin sheath of nerve fibers in the same way as they destroy the pellicles of red blood cells.

The relation of the hemolytic effects to the myelolytic effects of the four toxins may vary. Compared with saponin, cobra venom and streptolysin are more myelolytic than hemolytic, in test tube experiments, while the action of sodium taurocholate is similar to that of saponin, though potentially stronger.

The amount of saponin bound by 1 Gm. of spinal cord increases with the amount of saponin present. This phenomenon corresponds to the action of hemolytic amboceptors on red blood cells. The constants of Arrhenius' formula calculated for the saponin-cord system are relatively constant for final concentrations of more than 0.2 per cent.

The action of different lipids (lecithin, cephalin and galactolipids) on saponin was studied. It could be demonstrated that mixtures of equal parts of saponin and lipids did not reduce the hemolytic, myelolytic and toxic effects. Mixtures of one part saponin with five parts of the lipids were much less hemolytic. But while the combination with lecithin was also reduced in its myelolytic and toxic action, the combination of saponin with five parts of galactolipids had the same myelolytic and toxic effect as the 1 : 1 combination, if high toxic doses were used. The inhibitory effect of lecithin on sodium taurocholate was much more pronounced than the effect on saponin. Five parts of lecithin added to one part of sodium taurocholate completely inhibited the latter's hemolytic, myelolytic and toxic action.

Mixtures of saponin with red blood cells were no longer hemolytic and less myelolytic and toxic than the corresponding amount of saponin alone. Mixtures of saponin with emulsion of gray matter or emulsion of white matter of brains or emulsion of total brain substance were much less hemolytic and less myelolytic and toxic than saponin.

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16. Spitzer, H.: Arb. a .d. neurol. Inst. a. d. Wien. Univ. **28**:264, 1926.
17. Martin, J. P.: Brain **48**:162, 1925.
18. Laignel-Lavastine, M., and Koressios: Paris méd. **1**:190, 1929.

HUMAN INFECTION WITH ACTINOMYCES NECROPHORUS

BACTERIOLOGIC AND PATHOLOGIC REPORT OF TWO CASES TERMINATING FATALLY *

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Necrobacillosis, or infection with *Actinomyces necrophorus,* is relatively common in animals, but in man it is exceedingly rare. Descriptions of the disease and its wide occurrence in animals, of the characteristics and biology of *Act. necrophorus,* and of the pathology and bacteriology of the organism as observed in experiments may be found in the more or less exhaustive reports of Jensen [1] (1912), Weinberg and Ginsbourg [2] (1927) and Albrecht [3] (1929).

ANIMAL INFECTIONS

Veterinarians are familiar with the coagulation necroses and gangrene produced by the organism in the various animal tissues. Necrobacillosis has been described as responsible for the following common animal diseases: "calf diphtheria"; necrotic stomatitis of calves, lambs and pigs; "foot-rot" of cattle and sheep; gangrenous dermatitis—"grease-heel" and "necrotic quittor"—of horses and mules; the necrotizing ulcerations of the intestines in hog cholera (T. Smith, Bang), and multiple infarction abscesses in the lungs and livers of cattle and swine. The organism may spread by way of the lymphatics and produce metastatic nodular abscesses. Spontaneous necrobacillosis has been observed in more than fifteen animal species. It occurs in wild animals, such as the antelope, deer, kangeroo and ape. Chickens and birds have the disease, usually as avian diphtheria. Enzootic infections in guinea-pigs and rabbits have been reported. The disease in horses and mules is moderately fatal and has a high rate of morbidity. Postpartum necrobacillosis of the vagina and uterus of the cow occurring in epidemics

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1. Jensen, C. O.: Die vom Nekrosebacillus (Bacillus necroseos) hervorgerufenen Krankheiten, in Kolle and Wassermann: Handbuch der pathogenen Mikroorganismen **6**:234, 1913.

2. Weinberg, M., and Ginsbourg, R.: Données récentes sur les microbes anaérobies, Monograph de l'Institut Pasteur, no. 211, 1927.

3. Albrecht, B.: Infektionen durch Nekrosebacillen, in Kolle, Kraus and Uhlenhuth: Handbuch der pathogenen Mikroorganismen **6**:673, 1929.

and with a high mortality has been reported. Calves born of such animals frequently have so-called navel-ill or omphalophlebitis, with metastases to the liver.

The infection enters the body following injury to the skin or mucous membranes, and may spread by way of lymphatics or the blood stream to any of the body tissues. A similar pathologic process—localization of nests of the organisms, inflammation, formation of an abscess wall, necrosis, gangrene, sloughing, perhaps followed by healing—is observed in simple infections of the skin and mucous membrane. If the infection is not localized, thrombophlebitis results, and embolic metastases may occur to the viscera, bones and joints. These metastic infections are attended by infarction, necrosis and gangrene. Occasionally, proliferative changes occur. The spread through the lymphatics takes place most frequently in the lungs, where "daughter" nodules or abcesses are seen extending radially from a large central abscess. The liver is commonly infected by transmission of the organisms in the portal blood stream from primary infections in the intestines.

The early work of isolating and identifying *Actinomyces necrophorus* and correlating the lesions produced by it attracted the attention of some notable bacteriologists. Robert Koch, Loeffler, Theobald Smith, Bang and many others investigated the organism. Dammann probably first observed the clinical manifestation of *Act. necrophorus* in his investigation of diphtheritic infections in calves in 1876. He thought, however, that the disease was caused by *Bacillus diphtheriae.* Loeffler (1884) disproved this by showing that the predominating organism in the diphtheritic lesions was a gram-negative, thin rod with filamentous forms which he found on the border between the sound and the necrotic tissue. Koch had previously (1881) found an organism of similar morphology in the sweat glands of sheep having "sheeppox." Shutz (1888) found similar filiform bacilli in the livers of cattle, and succeeded in transferring them into rabbits and mice. Theobald Smith (1889) saw long, gram-negative bacilli in the intestinal lesions of hog cholera. In 1890, Bang identified the organism in hog cholera, and gave it the name "nekrosebazillus." Schmorl [4] (1891) isolated and cultured, for the first time, the same organism from necrotic lesions of rabbits during a virulent epizootic. Numerous other workers have subsequently confirmed these results and have investigated the morphologic, cultural and pathologic characteristics of *Act. necrophorus* in animals.

HUMAN INFECTION

Instances of authentic infection with *Act. necrophorus* in man are rare. There are in the literature several presumptive reports of acute

4. Schmorl, G.: Ueber ein pathogenes Fadenbacterium (Streptothrix cuniculi), Deutsche Ztschr. f. Thiermed. **17**:375, 1891.

infection with *Act. necrophorus* following exposure to animals with necrobacillosis. These were usually instances in which veterinarians had attacks consisting of chills and fever, malaise, weakness, thirst and dysphagia, and showing a pharyngeal membrane (Dammann, Casper and Schumann). No cultures were taken. Recovery followed. Hutyra-Marek similarly observed linseed-sized nodules on the hands of a shepherd occurring during an enzootic of necrobacillosis in a herd of sheep. The lesions ulcerated in three or four days, and in ten days had healed completely. Ellermann [5] (1905) more nearly approached a diagnosis of necrobacillosis in reporting the case of a 9-months old infant dying with pseudo-diphtheria, laryngitis and penumonia. Culture of the necrotic membrane failed to reveal diphtheria bacilli, but sections of the uvula showed long, threadlike, gram-negative bacteria in the caseous tissue nearest the living structures. The strong resemblance of these bacilli to *Act. necrophorus* and the similarity of the lesions to those of "calf diphtheria," in the absence of a positive culture for *B. diphtheriae,* caused him to suggest this as a case of primary infection with *Act. necrophorus.* Reiner Müller found similar organisms in the mucous membrane of a girl with angina.

Apparently, there are on record only three reports of proved infection with *Act. necrophorus* in man. The cases were all of infection in the skin. Schmorl [4] (1891) himself and one of his assistants each had a small abscess on one finger from handling rabbits with spontaneous and experimental necrobacillosis. Stained smears of the pus showed the characteristic gram-negative filiform bacteria originally cultivated and described by him. The lesions were chronic and healed slowly. Steman and Shaw [6] (1910) and Shaw [7] (1925) isolated the organism in pure culture from the large necrotic vesicles of a lesion on the hand of a government meat inspector. The patient, while dissecting an ulceration on the lip of a sheep, had accidentally scratched his left hand on one of the sheep's teeth. Following this injury there was local redness, with swelling and severe pain. When the patient was examined by the authors, he had, over the back of the left hand, an extensive area of coagulation necrosis, accompanied by large vesicles. The entire left extremity was swollen to the shoulder. The color of the lesion varied between gray and purple. The lesion measured 2½ by 2 inches (6.27 by 5 cm.), with a highest elevation of about ¾ inch (1.83 cm.), and was grayish-purple. Treatment consisted of free drainage and moist

5. Ellermann, V.: Einige Fälle von bakterieller Nekrose beim Menschen, Centralbl. f. Bakteriol. I, O. **38**:383, 1905.

6. Steman, C. M., and Shaw, F. W.: Necrobacillosis of the Skin, J. Kansas M. Soc. **10**:405, 1910.

7. Shaw, F. W.: Necrobacillosis, Bull. Medical College of Virginia, March, 1925.

antiseptic packs. The patient had a temperature as high as 39.4 C. (102.9 F.) for one week; in three weeks, the wound had entirely healed. The third case of human infection is reported by Van Wering [8] (1923). *Act. necrophorus* was isolated in pure culture from a lesion on the forearm of a man who had been bitten by a cow. He had a temperature ranging between 38 and 39 C. (100.4 to 102.2 F.), a cluster of small abscesses on the forearm and lymphangitis and axillary lymphadenitis. A bluish discoloration appeared, and the lesion became necrotic in the center and possessed a raised rim of indurated granulation tissue. The culture of the organism was obtained from tissue excised from this border area after cauterization. After varied, nonsurgical treatment the lesion healed.

Two additional cases of necrobacillosis in man, both terminating fatally, presenting hitherto undescribed clinical and pathologic features of systemic infection in man, and verified by bacteriologic studies, are described in the following paragraphs.

REPORT OF CASES

CASE 1.—*History.*—B. M., a white girl, aged 19, unmarried, a clerk, was admitted to the medical service of the Strong Memorial Hospital at midnight, Dec. 25, 1928, complaining of weakness, malaise and fever. Symptoms were first noticed with the onset of malaise, ten days before. Two days later, headache and feverishness were complained of. The following day, seven days before admission, the patient was forced to bed feeling extremely ill. She had, in addition to the symptoms previously noted, three severe chills in succession and a temperature as high as 103 F. (39.4 C.), accompanied by sore throat, pain throughout the neck, shoulders and back, and inability to retain food or fluids. Photophobia and ocular pruritus were present. These symptoms persisted, with high fever, vomiting and daily chills. On the seventh day, there was a slight remission. On the eighth day the sore throat had disappeared; however, a marked exacerbation of all symptoms occurred, with fever as high as 105 F. (40.6 C.). On the tenth day (the day of admission), the patient complained of severe pain in the region of the left hip.

The patient's general health had always been good. She had had measles, mumps, varicella and influenza in childhood, and swelling of the cervical glands for a few days three months previous to admission. Five months before admission, the patient had been delivered, without complication, of a normal, full-term child.

Physical Examination.—On admission, the patient lay quietly in bed, appearing well-nourished, fairly comfortable, alert and cooperative. The temperature was 40.3 C. (104.5 F.); the pulse rate was 84, and the respiration rate, 24. The skin was hot and dry without petechiae or eruptions. Breathing was somewhat labored and rapid. The patient had no immediate complaint aside from pain in the left hip on movement of the left thigh. There was moderate enlargement of the cervical group of lymph nodes. The sclerae were subicteric; the eyes were otherwise normal. There were herpetic crusts around the nose and over the lips. The

8. Van Wering, F.: Over een geval van besmetting met den necrosebacil van Jensen, Nederl. Tijdschr. v. Geneesk. **1**:2892 (June) 1923.

tongue was moderately coated, and the oral mucous membranes showed injection and were dry. The pharynx was deeply inflamed, especially over the anterior pillars; on the posterior wall, a mucopurulent exudate was present. The tonsils were small but inflamed. The lungs were clear, with from 22 to 24 respirations a minute. The heart was normal. The blood pressure was 110 systolic and 50 diastolic. The abdomen was unremarkable, except for striae albae of pregnancy. The results of rectal and pelvic examinations were negative. Extreme pain was felt in the left hip during flexion of the thighs. Palpation over the left hip joint revealed tenderness over the region posterior and superior to the trochanteric eminence. There was also some pain on pressure just below the left inguinal ligament. Extension and flexion of the left thigh produced pain referred to the hip, but no pain followed internal and external rotation of the limb. Pain was present on palpation over the left sacro-iliac joint. The reflexes were normal.

Laboratory Observations.—The urine was yellow and cloudy, and contained a slight trace of albumin and a moderate number of hyaline and granular casts, a few leukocytes and an occasional red blood corpuscle. The hemoglobin content of the blood was 85 per cent (Sahli); the leukocyte count, 16,400. The smear was normal. The differential count showed: polymorphonuclears, 92 per cent; lymphocytes, 6 per cent, and large mononuclears, 2 per cent. The nonprotein nitrogen was 45.8 mg. per hundred cubic centimeters. The blood Wassermann reaction was negative. The result of the Widal test was negative. A culture of urine contained *B. coli.* Cultures from throat smears showed about 10 per cent hemolytic streptococci. Three blood cultures gave no growth to the time of death. Stereoroentgenograms of the pelvis (taken the day after admission) showed nothing definite except for slight irregularities and haziness along the left sacro-iliac joint and generalized clouding of the left hip joint; a flat plate of the chest showed only accentuated hilum shadows on the right. Exposures taken three days later (fourth day after admission) showed shadows of increased density near the right hilum on a level with the seventh and eighth dorsal vertebrae, not typical, however, of consolidation; and stereoscopic photographs of the sacro-iliac joints showed some fuzziness but no definite clearcut changes (fig. 1).

Course.—On the morning of admission, the patient had a temperature of 40.4 C. (104.7 F.), a pulse rate of 122 and a respiration rate of 28. The first impression was that she had a streptococcus sore throat, septicemia, pneumonia or a septic process involving the left hip joint. The orthopedic consultant who saw the patient on the day after admission thought the physical observations suggested involvement of the left sacro-iliac joint; the signs, however, were not at all typical. Slight fulness and tenderness were apparent over the left sacro-iliac joint and pain in the inguinal region on flexion of the straight limb beyond 45 degrees; no tenderness was felt on deep pressure in the left lower quadrant of the abdomen. On the third day, the patient was more toxic, and at times delirious, her condition suggesting pneumonia despite the absence of signs in the chest other than accentuated breathing in the upper right region. The local signs in the left sacro-iliac region were more definite, with tenderness in the left lower quadrant. The orthopedist's decision was to postpone surgical intervention until pneumonia was ruled out. At this time, the skin assumed an icteric tint. The temperature remained sustained around 39 C.

During the next two days, the patient became worse. The temperature was 41.3 ± C. (106.3 F), the pulse from 130 to 160 and the respirations from 22 to 44. The local signs around the sacro-iliac region were accentuated and then they completely disappeared. Surgical procedures were then deemed unnecessary.

The roentgenologist reported only slightly increased shadows in the hilum region on the right. Meanwhile over the coccyx two small gangrenous ulcers containing minute hemorrhages had appeared. Lumbar puncture showed normal spinal fluid. Repeated examinations by various medical consultants failed to yield any additional information. Daily leukocyte counts ranged between 19,000 and 23,000 per cubic millimeter. Several examinations of the urine gave the same results as on admission. Several blood smears were similar, except for a marked decrease in the number of platelets seen. From day to day, the patient became more toxic. The hyperpyrexia, chills, jaundice and irregular irrational state continued. Fluids were

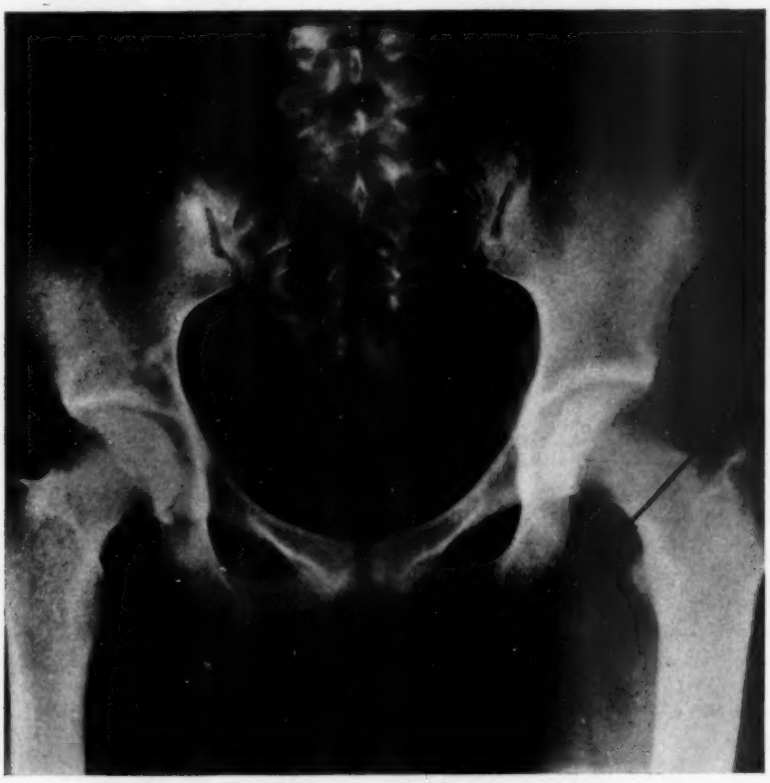

Fig. 1 (case 1).—Roentgenogram of pelvis, Dec. 28, 1929. A rarefied "string" of air in the soft tissues can be seen medial and anterior to the neck of the left femur and the lesser trochanter. The left sacro-iliac and hip-joints show only slight general cloudiness.

forced, and infusions and sedatives given. On the fifth day, a definite friction rub, accompanied by fine râles, was heard over the right side of the chest posteriorly from the seventh to the ninth ribs about 5 to 6 cm. from the vertebral margin. A blood smear showed polymorphonuclears 93 per cent with many young forms, myelocytes 2 per cent, lymphocytes 3 per cent, large mononuclears 2 per cent and no blood parasites.

On the sixth day, the patient was still worse. Deep jaundice set in. The icteric index was 125 (12.5 mg. per hundred cubic centimeters bilirubin). The local signs in the region of the hip had disappeared or were masked by the toxic state of the patient. On the seventh day, it was decided to employ transfusion. At this time the blood showed: leukocytes 10,400, hemoglobin content 110 per cent (Sahli), red cells 5,500,000 and a diminished number of platelets in the smear. The patient had become moribund, with a temperature of 41.7 C. (107.1 F.), cyanosis and a rapid, weak pulse. Cardiac stimulants were ineffective. As a transfusion was being prepared, death occurred at 2:20 p. m., Dec. 31, 1928.

Antemortem Diagnosis.—General sepsis; ? pylephlebitis; ? Weil's disease.

Necropsy.—Postmortem examination was performed by Dr. Khun Shribishaj one hour after the patient's death. The anatomic diagnosis was: Retroperitoneal abscess (left) involving sacro-iliac joint, hip joint and upper part of leg; infarction of lungs with abscess formation; fibrinous pleuritis; acute bronchitis; hemorrhagic enteritis; adhesive salpingitis; acute splenic tumor; slight cloudy swelling of the liver and kidneys; jaundice; skin hemorrhage (coccygeal region) and ecchymoses (abdomen and thighs).

The body was warm and emaciated, and the skin of a deep icteric color. Over the coccygeal region was a bluish-red hemorrhagic area of induration measuring 10 cm. in diameter. The sclerae were also icteric. There was no lymphadenopathy. The serous surfaces were generally smooth and had an icteric tint. There was no excess of fluid in the peritoneal, pericardial or pleural cavities. There were fibrinous pleural adhesions over the lateral and posterior aspect of the lower and middle lobes of the right lung. In this region, the pleural surfaces were roughened and showed injection. The liver margin extended 1 cm. below the right costal border in the midclavicular line.

The heart weighed 200 Gm. and was normal, except for several hemorrhagic spots over the endocardium. The blood in the heart chambers was a thin, pale red liquid and clotted slowly.

The right lung weighed 370 Gm., the left 250 Gm. The right lung was soft and bluish gray, except for a large area about 8 cm. in diameter over the middle portion externally and a few areas varying from 1 to 3 cm. in diameter over the basal margins. These areas were deep red and firm, appeared to have soft gray centers and were covered with a roughened coat of yellowish fibrin. Those at the base of the lung appeared to be typical abscesses. Many petechial hemorrhages were scattered over the entire lung surface. The peribronchial lymph nodes were slightly enlarged, softened and bluish-gray. The bronchi contained a yellowish-gray mucopurulent exudate, and the mucosa showed injection, and was swollen and yellowish pink. Sections of this lung showed several large and small areas of infarction throughout the middle and lower lobes. The largest one corresponded to the previously mentioned firm area over the middle portion of the lung, and extended inward about 6 cm. from the lung surface. This infarct was firm, had a deep red, elevated surface with a grayish-pink necrotic center. Mucopurulent material exuded on pressure. The smaller infarcts were similar. Over the base of the lung toward the margins were a few additional abscesses, varying from 1 to 2 cm. in diameter, containing thick, greenish-gray pus, and having thin, well-defined walls. No thrombi were seen in the larger vessels adjacent to the abscesses or infarcts. Other portions of the lung were soft, pinkish-gray, moist and crepitant. The left lung also was bluish gray, and its surfaces were mottled with many petechial hemorrhages. A few translucent, yellow, fibrinous patches were scattered over the basal margins. With the exception of a large infarction, the left lung resembled the right.

The spleen was enlarged (240 Gm.), and its capsule was tense and smooth. On section, the soft bulging appearance of acute splenic tumor was seen.

The liver, pancreas, appendix, brain and blood vessels were normal.

The stomach contained dirty black, viscous mucus. The mucous membrane of the entire gastro-intestinal tract was normal, except for a portion of the ileum 15 cm. in length a half meter from the cecum. Here the mucosa, especially about the rugae, was deep red, swollen and covered with bluish-gray necrotic tissue.

The transition between the cortex and medulla of the suprarenal glands was indistinct, and the medulla seemed rather soft.

The pyramids of the left kidney were red, showed injection and were sunken. Otherwise, the kidneys, as well as the bladder and ureters, were normal.

The uterus was of normal size. It was hemorrhagic in a small area (old placental site) in the fundus. The lateral half of the left fallopian tube was swollen and soft and showed injection. The fimbria was also swollen, deep red and adherent to the ovary by a small cystlike sac containing translucent, yellowish mucus. The broad ligament and ovary were normal. The right adnexa and the vagina were normal.

In the retroperitoneal tissues behind the left kidney was a large, swollen, jelly-like abscess containing thin, pinkish-gray pus with bluish-gray necrotic tissue. This abscess had no definite wall, but extended downward along the left psoas magnus fascis and intermuscular connective tissue septums. The left psoas magnus muscle was swollen and softened, and the muscle tissue in places appeared bluish, soft and necrotic. From this muscle, the abscess was traced into the left pelvic connective tissue and muscle fascia downward into the left sacro-iliac and hip joints, and half the length of the femur. The left hip joint, when opened, seemed to contain gas under pressure. The hip joint capsule and periosteum were bluish and necrotic. The joint cavity was distended with thin, bluish-gray pus possessing a peculiarly foul odor. The right hip joint was not investigated, but the structures and fascias of the right side of the pelvis seemed normal. The lumbar vertebrae, sacrum and upper end of the left femur showed no abscesses or inflammation. There were no thrombi in the left common iliac, femoral or ovarian veins.

Microscopic Examination.—Sections of the heart showed some swelling and opacity of the muscle fibers. In the lungs were many abscesses of varying size. The walls of the larger abscesses consisted of newly formed fibrous tissue rich in young blood vessels and infiltrated with polymorphonuclear leukocytes. These walls were covered with necrotic cellular débris and clumps of bacteria. The small abscesses had no definite walls and consisted of leukocytes and clumps of bacteria. The alveoli and bronchial walls were engorged with blood, and in several areas contained an acute cellular exudate. There was marked dilatation of the intact alveoli.

The spleen showed blood engorgement in the sinuses and stroma; increase in leukocytes and plasma cells, and hyperplasia of the mononuclear elements of the splenic tissue. The liver cells were swollen, and the cytoplasm opaque and finely granular.

Sections of pancreas, ovary, brain and pituitary were normal; also the uterus, except for hemorrhage into the mucosa in the region of the placental site.

The intestine showed diffuse hemorrhages into the mucosa.

The suprarenal glands showed a scattering infiltration with clusters of small lymphocytes and plasma cells. In places beneath the capsule there were small necrotic cells surrounded by polymorphonuclear leukocytes.

The kidney tubules showed cloudy swelling. The capsule was thickened and fibrotic in places with cellular infiltration, consisting mainly of lymphocytes.

The left fallopian tube showed a diffuse cellular invasion into the submucous and muscular coats.

Sections of the psoas muscle revealed abscess walls covered with necrotic, poorly preserved, bluish-staining, homogeneous material and polymorphonuclear cells. Adjacent muscle fibers were swollen, opaque and indistinct. Along the muscle septums much acute cellular exudate and fibrin were seen. Edema and hemorrhage were prevalent.

Sections of the hip joint capsule showed necrosis, hemorrhage and polymorphonuclear infiltration into the serosa. There were many clusters of bacteria in the blood vessels and probably in the lymph channels of the submucosa. Diffusely scattered clumps of coarse, dark brown material were seen everywhere.

Bacteriology.—From the psoas muscle, pus and lung infarcts, small, short, gram-negative bacilli were seen on smear; and from these materials and the blood, pure anaerobic cultures of a gram-negative, thin, pleomorphic, filamentous coccobacillus were obtained. Antemortem blood cultures also yielded a similar organism, but not before death. A gram-positive diphtheroid grew out in the aerobic cultures of the lung infarct.

CASE 2.—*History.*—F. C. G., a white man, aged 64, a clothing cutter, was admitted to the surgical service, emergency division, of the Strong Memorial Hospital, Feb. 13, 1929. He chiefly complained of sore throat, chills, fever and dyspnea. The onset had occurred three days before when the patient complained of a sore throat. At that time, his neck was swollen, and the left tonsil seemed distended and swollen to almost midway in the pharynx. The next day the family physician was called. He thought the patient had quinsy. During that evening, chills and fever appeared. By the following morning (the day of admission), the temperature was normal, but the patient's wife noticed that he had great difficulty in breathing. His physician, when summoned, advised immediate hospitalization.

The patient had been troubled with hoarseness, at intervals, for the previous twenty years, and had had a growth removed from his pharynx by a local specialist prior to this time. He had gonorrhea in his youth. He had a bilateral inguinal hernia repaired in this hospital in 1927. At that time, the diagnosis was chronic myocarditis and general arteriosclerosis.

Physical Examination.—On admission, the patient was breathing with great difficulty. The temperature was 36.5 C. (97.7 F.); the pulse rate was 96, the respiration rate 30. There was retraction of the chest during respiration, and there was swelling of the neck, with (crepitant) emphysema over the left side down to the clavicle. The lungs seemed clear. The impression of the physician who admitted the patient was that there was a perforation of some air passage, probably the larynx or the trachea. A surgical consultant confirmed the observations already noted. The swelling of the neck was diffuse, involving the whole left side. The left tonsil was moderately enlarged, and both arytenoid cartilages and the aryepiglottic fold and the false vocal cords were swollen. The right true vocal cord was moderately swollen and showed injection; the left could not be seen. Percussion of the chest revealed no areas of dulness, but both sides were slightly hyperresonant. Sibilant râles were heard in both bases. The clinical impression was: emphysema and abscess of the left side of the neck, possibly secondary to a left peritonsillar abscess. Immediate tracheotomy was advised.

Laboratory Observations (Emergency).—The blood showed red blood cells, 4,850,000; hemoglobin content (Sahli), 100 per cent; leukocytes, 4,900 per cubic millimeter. The differential count showed: polymorphonuclears, 83 per cent; lymphocytes, 3 per cent, and mononuclears and transitions, 14 per cent. The smear revealed practically no mature polymorphonuclears, nearly all being in the metamyelocytic and related forms. A roentgen ray picture of the chest showed shadows of decreased density in the left supraclavicular and left cervical region, suggesting

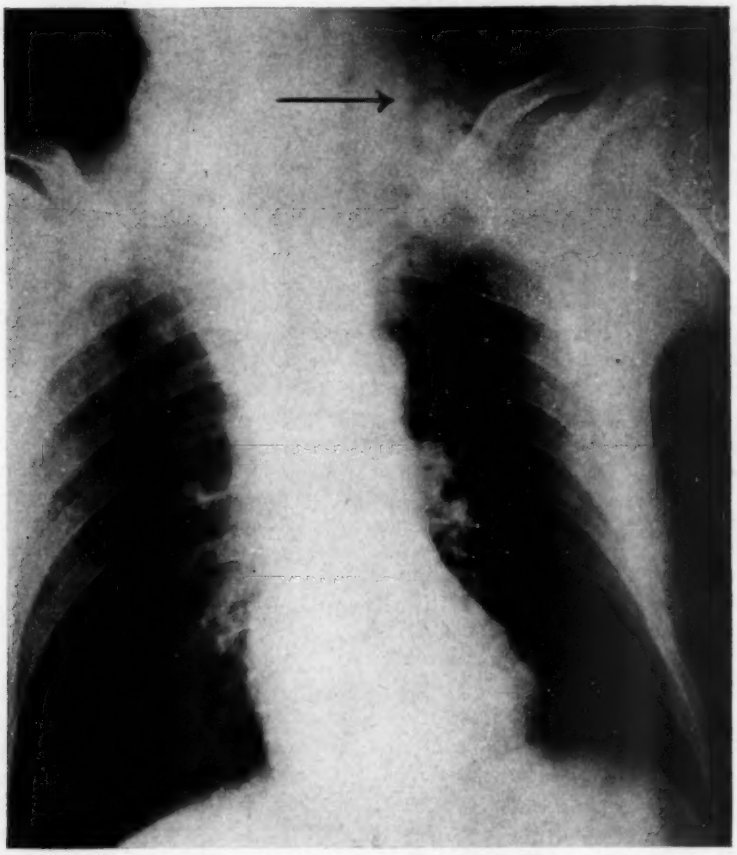

Fig. 2 (case 2).—Roentgenogram of chest, Feb. 13, 1929. "Pocketed rarefactions" due to interstitial emphysema can be seen in the left cervical and clavicular regions to a point several centimeters below the clavicle.

interstitial emphysema of the soft parts probably from a rupture of either the upper portion of the esophagus or the larynx (fig. 2).

Course.—The patient was taken to the operating division, where, under procaine hydrochloride anesthesia, a tracheotomy was performed. A low collar incision was made, and the skin fascia and platysma muscle were deflected. An abscess containing a foul, greenish-brown, watery pus was encountered beneath the fascia of the left sternohyoid and sternothyroid muscles. A smaller abscess was present on the right. A tracheotomy tube was inserted through an incision in the second

and third cartilages. Immediate respiratory relief for the patient resulted. Petrolatum gauze pack and dry dressing were applied.

Despite the immediate respiratory relief following the operation, the patient's condition was considered critical. Steam inhalations and rectal infusions of 5 per cent dextrose were given. Early the next morning the pulse became weak and rapid, the respirations rapid and labored, and the temperature rose to 39 C. (102.2 F.). Percussion dulness and râles were noted at both lung bases. Ephedrine, epinephrine and caffeine were administered without improving the condition of the patient, and he expired at 9 a. m. Feb. 14, 1929.

Antemortem Diagnosis.—Abscess and emphysema of neck.

Necropsy.—Postmortem examination was performed by Dr. George H. Whipple four hours after the patient's death. The anatomic diagnosis was: Retropharyngeal abscess with gangrene and extension into the peritracheal and subcutaneous tissues as well as the upper anterior and posterior mediastinum; operative incision and tracheotomy wound; acute purulent pleurisy, both lungs; acute fibrinous pericarditis; acute tracheitis and bronchitis; bronchopneumonia; pulmonary edema; emphysema; fibroid apical scars, both lungs; healed surgical incisions (inguinal herniae); arteriosclerosis; diverticulum of cecum.

The body was rather slender. It was discolored by livor mortis and rigor was well marked. The neck, especially on the left, was considerably swollen, and gave diffuse crepitation. The recent surgical incision extended about 10 cm. around the neck somewhat below the cricoid cartilage. In this wound was exposed a dirty, greenish-brown, gangrenous area from which a foul, greenish, watery pus exuded, and an opening (tracheotomy incision) was seen entering the trachea. Scars of the repair of the inguinal hernia were present. The peritoneal surfaces were normal, except for a few adhesions between the sigmoid and the left obliterated inguinal sac.

When the manubrium was removed, the area of inflammation with gangrene extended down about 2 inches (5 cm.) below the manubrium into the anterior mediastinum. Below this and extending over the pericardium, there was edema with some infiltration of the wet tissue with gas bubbles. The pericardial sac was involved in this acute process, which had extended through it. The sac was thickened, and its inner surface slightly roughened, showing a little fibrin and mottled reddish spots. A slight excess of pericardial fluid was present. In the left pleural cavity there was about 100 cc. of turbid serous fluid, and some purulent exudate was adherent to the posterior portion of the left lung. This was true also of the right lung. A few old apical adhesions were present.

The heart weighed 370 Gm. The epicardium anteriorly showed early pericarditis, with some injection and a few ecchymotic specks and grains of fibrin. Except for small patches of arteriosclerosis on the aortic valves and in the coronary arteries, the heart was normal.

The left lung weighed 600 Gm., and the right 480 Gm. The inflammatory process from the mediastinum extended into the tissues about the left hilum. The bronchi showed injection and contained some purulent exudate. The pulmonary vessels were normal. In the left lung, the upper lobe was somewhat moist and, on section, was mottled with a greenish color. There was no consolidation. There were some areas of collapse alternating with areas of emphysema in the left lower lobe. The wet red lung tissue seemed to possess a little cellular exudate, but no well marked areas of consolidation. Practically identical observations were made in the right lung. In the lower lobe of the latter were a few indefinite grayish areas suggesting early bronchopneumonia.

The spleen, pancreas and suprarenal glands appeared normal.

The liver weighed 1,700 Gm. It possessed a somewhat yellowish cast when viewed through the capsule.

The gastro-intestinal tract was normal, except for several small submucous hemorrhages in the ileum and a diverticulum 2 cm. in diameter in the cecum.

The kidneys weighed 150 and 160 Gm. They contained a few small cysts but otherwise were normal.

The bladder and prostate were normal, except for slight enlargement of the latter.

The vascular system showed a moderate amount of arteriosclerosis in the aorta.

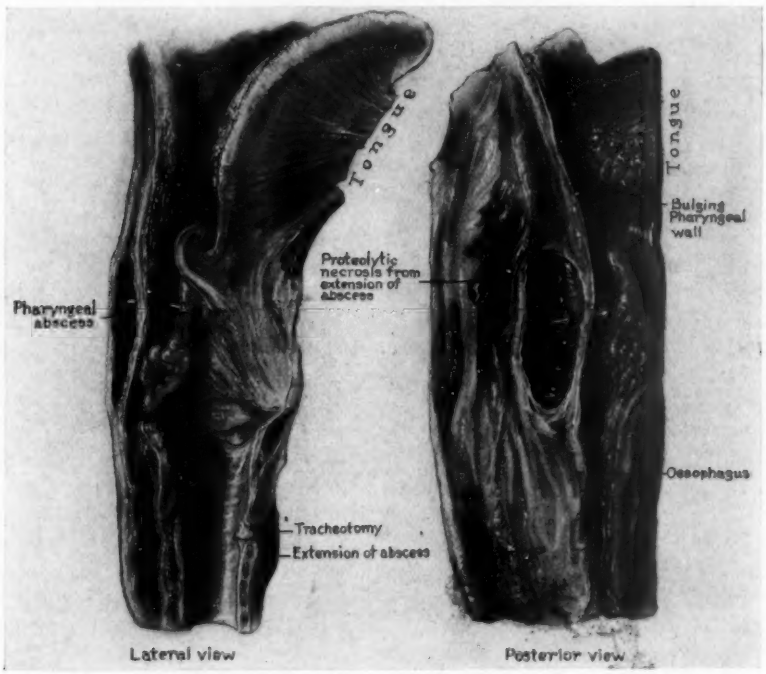

Fig. 3 (case 2).—Lateral and posterior views of the fixed museum specimen of organs of the neck. The large pocket of the retropharyngeal abscess, the opening from the pharynx, the proteolysis of the adjacent tissues, and the edema of the pharyngeal wall, epiglottis and subepiglottid structures should be noted.

Organs of the Neck: The thyroid, embedded in a mass of gangrenous semi-digested material, appeared intact and, on section, normal. The large vessels were clear. When the esophagus was opened from behind, it appeared to be normal as far as the region just above the cricoid cartilage (fig. 3). Here to the left of the midline there was a discolored area about 5 cm. in length. Behind this area were communicating pockets showing necrosis and greenish slough. One of these pockets communicated by a small opening with the pharynx. The tonsils were normal. The tissues on the left side of the throat, including the soft palate, were edematous, having a jelly-like, semitranslucent appearance. The edema was

marked on the left side of the epiglottis and in the aryepiglottic folds. The right side of the epiglottis was relatively normal, as well as the remaining pharyngeal structures on the right side. The tongue was normal. The trachea was normal, except for the tracheotomy opening. On the left there was marked edema with induration and communicating pockets of necrosis infiltrating the tissues adjacent to the pharynx and the operative incision previously described. The retropharyngeal space was almost completely involved in this process extending down as far as the arch of the aorta.

Microscopic Examination.—Some sections of the lungs showed anthracosis and areas of atelectasis; some showed edema and clusters of bacteria in the acini and exudate of polymorphonuclears; and others, pleural inflammation in which masses of bacteria were conspicuous. In the mediastinum there was persistent thymus tissue with cystic areas and acute inflammation with colonies of bacteria. The aorta showed atheroma with subintimal degeneration; the kidney, a few scattered arteriosclerotic scars; the stomach, a slight degree of chronic gastritis; the thyroid, a few small adenomas; and the prostate, some hypertrophy and numerous corpora amylacea. The suprarenal glands, spleen and pancreas appeared normal.

Microscopically, the tissues of the neck and pharynx showed extensive necrosis of the muscle fibers with hyaline change and a typical cellulitis with masses of bacteria. One vessel showed inflammation of the wall extending inward almost into the subintimal tissue. No thrombi were present. The thyroid showed no inflammation.

Bacteriology.—From the foul, greenish pus from the neck tissues, *Pneumococcus* type IV was identified; a nonhemolytic, anaerobic, short-chain streptococcus was grown; and a gram-negative, thin, pleomorphic, filamentous, anaerobic coccobacillus was isolated. A similar gram-negative, thin, pleomorphic, filamentous, anaerobic organism was obtained from cultures of the pericardial purulent exudate, accompanied by an occasional anaerobic, nonhemolytic, short chain streptococcus. A gram-positive bacillus was present in the smears of the pus from the neck, but did not grow out in cultures. Spore-bearing organisms were not present. The gram-negative bacilli appeared in the smears as small short rods having deeper staining terminal polar bodies. Spirochetes were not seen in the smears from the subcutaneous abscess.

BACTERIOLOGY OF ACTINOMYCES NECROPHORUS

Original cultures of material obtained at both necropsies were made in a series of duplicate poured plates of 5 per cent (rabbit) blood agar for observing parallel growth of aerobic and anaerobic organisms. Anaerobic cultures were maintained in the jar described by Brown.[9] In case 1, *Actinomyces necrophorus* was secured in pure culture, except for the gram-positive, aerobic diphtheroid, probably a contaminant, derived from the lung infarct. In the second case, the wound constituting the portal of entry (retropharyngeal abscess) gave ready access to other (secondary) organisms. These bacteria were present in small numbers, as the smears and cultures indicated.

9. Brown, J. H.: An Improved Anaerobe Jar, J. Exper. Med. **33**:677, 1921.

It has been pointed out that the most frequent entry of *Actinomyces necrophorus* into the body is either through the skin or the mucous membranes. Harris and Brown [10] found the uterus the portal of entry for infection with *Act. pseudo-necrophorus*, an organism similar in morphology to *Act. necrophorus*. The relatively normal 5 months old placental site found at necropsy in case 1 was therefore at first suspected as the origin of the infection. After reviewing the observations at necropsy, weeks later, the 15 cm. long bluish, hemorrhagic ulceration of the lower ileum appeared to have been the more probable portal of entry. In case 2, the small ulcerous opening into the retropharyngeal abscess was obviously the most conspicuous connection between mucous membranes and the extensive proteolytic process. Unfortunately, smears and cultures were not obtained from uterus, intestine, or pharynx, to check the bacterial flora at these points.

Studies on the morphology, cultural characteristics and serology of the strains of *Act. necrophorus* isolated in these two cases were made, unfortunately, without an acquaintance with the organism. No strains were available from any source for comparison. But the identification of the organism was confirmed through the kindness of Dr. J. Howard Brown,[11] who examined strains from each case. On the other hand, Dr. W. A. Hagan,[11] of Cornell, expressed some doubt as to whether these were cultures of true *Actinomyces necrophorus*. The organisms isolated from these cases, however, appeared to satisfy most of the essential criteria used to identify *Act. necrophorus*.

Morphology and Staining.—The organisms as obtained from the pus from human tissues appeared as short, bipolar, gram-negative, minute coccobacilli with rounded ends or as slightly longer, solid-staining rods. In one instance, they were not distinguishable from the cellular débris until another search was made. Then there were discovered also occasional weblike clusters of gram-negative strands and longer rods having fairly regularly arranged, deeper staining coccoid bodies. In cultures, the organisms were nonmotile and occurred in the most bizarre forms. In addition to those just described, they were seen as long filaments in great tangled masses, with fairly regular, deep-staining coccus-like granulates (fig. 4). The filaments sometimes extended nearly across the oil immersion field. In some, especially the shorter rods, the staining was more irregular, assuming the appearance of biconcave partitions of variable thickness, separating slightly swollen or bulbous compartments. In these, the ends were frequently pointed,

10. Harris, J. W., and Brown, J. H.: Description of a New Organism That May Be a Factor in the Causation of Puerperal Infection, Bull. Johns Hopkins Hosp. **40**:203, 1927.

11. Personal communication.

like the bow of a narrow boat, and terminal polar bodies were usually present. The filamentous forms were more numerous on solid mediums, at times stained solidly, or as segments with empty compartments, some of which were bulbous (fig. 5). The organisms took the aniline stains, and with methylene-blue, solid-staining diphtheroids or forms with club-shaped extremities were seen. In the older cultures and occasionally in the young, the pleomorphism and "vacuole" formation were most spectacular. Spores were not formed. Large "trunks" were seen, from

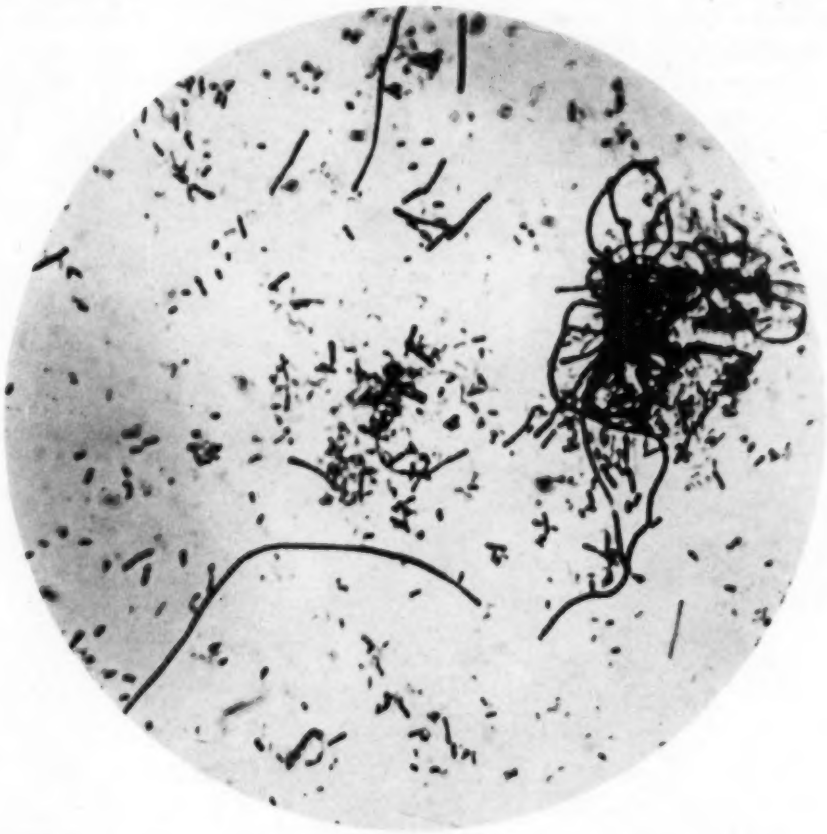

Fig. 4.—Photomicrograph of methylene blue stained smear from a two to three day old blood agar culture of Act. necrophorus A-718 M. showing long curled, filamentous forms with pleomorphic short rods.

which small branches or "twigs" appeared to radiate. The deep-staining granules were arranged irregularly near the periphery of the "trunk" and as small cocci filling the "sheath" of the branches. A terminal polar body was commonly present in each branch. Large clubbed filaments with smaller granules were sometimes seen. Acute fusiform dilatations were occasionally present in the filaments, or the rods some-

times assumed a short swollen form in which the polar staining was in the form of a thin crescent. Occasionally, terminal bulbous enlargements were present. Schmorl's [4] excellent illustrations are characteristic of many of the morphologic variations observed in these strains of *Act. necrophorus.*

Cultural Characteristics.—On appropriate mediums kept anaerobically at 37 C., *Act. necrophorus* survived as long as five months. Optimum growth was obtained on mediums containing ascitic or hydrocele fluid.

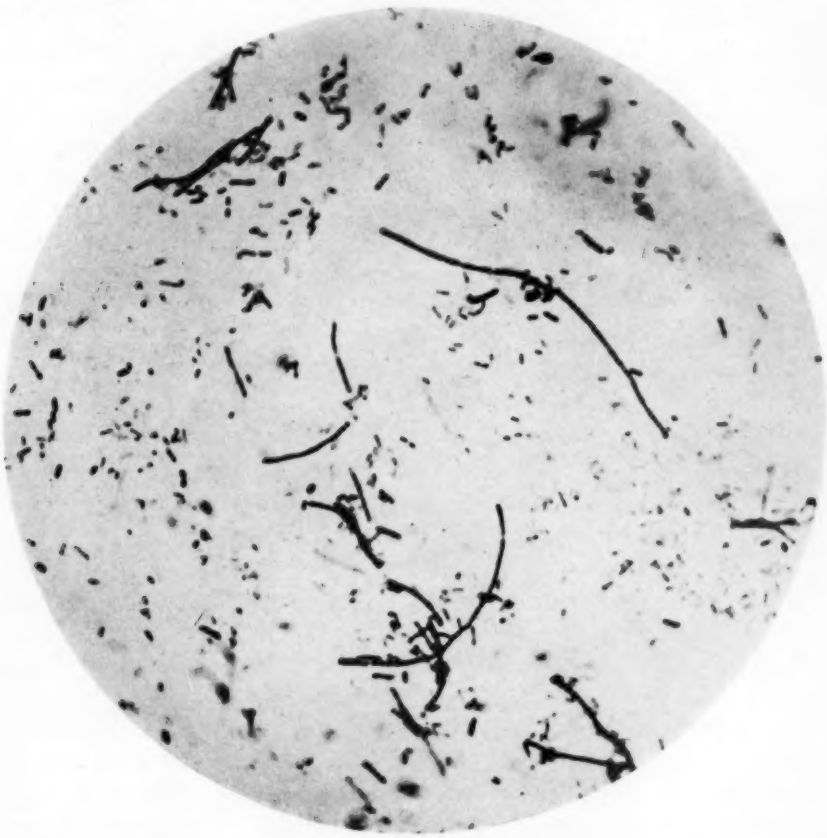

Fig. 5.—Photomicrograph of methylene blue stained smear from a two to three days old blood agar culture of Act. necrophorus A-718 M, showing several filaments with cross-striations and bulbous compartments.

The organism was an obligate anaerobe. Growth in tubes of cooked meat (Douglas' tryptic broth) medium with a petrolatum seal was accompanied by a moderate production of foul gas without appreciable digestion of the particles of meat. At first in this medium there was a flocculent, fuzzy growth which later settled to the bottom of the tube, where it had a pale blue appearance among the particles of meat. On

5 per cent blood agar plates, a wide zone of beta hemolysis appeared in from 24 to 48 hours (fig. 6) with smooth, convex-topped, nearly transparent surface colonies having fairly regular edges and a slightly brownish center. Three-day colonies measured from 2 to 3 mm. in diameter. Older surface colonies showed serrated or fuzzy filamentous edges. These projected radially from a darker rim zone separated by a lighter intermediate zone, and were surrounded by a finely granular brownish area superimposed on the clear, hemolyzed plate (fig. 7). Such colonies measured between 3 and 7 mm. in diameter. A foul odor was also produced by the growth on blood agar plates. Colonies growing deep in blood agar tubes or plates appeared as yellowish-gray, dirty, biconvex lenses, surrounded by hemolysis and a brownish discoloration.

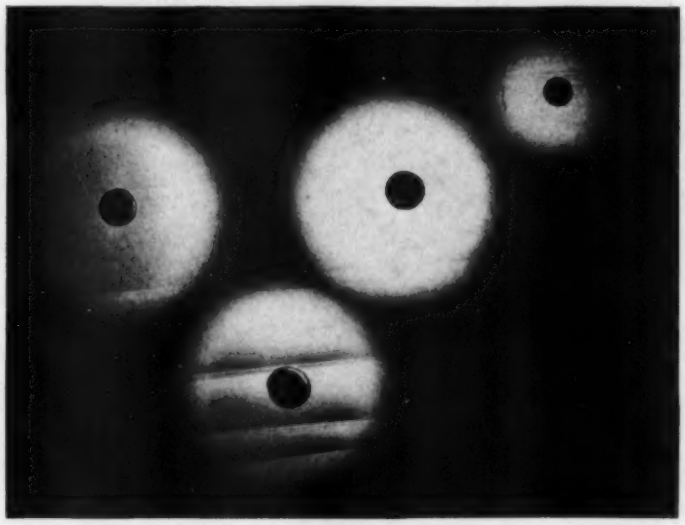

Fig. 6.—Surface colonies of Act. necrophorus A-718 M, on a blood agar plate, from two to three days old. The wide zone of hemolysis should be noted.

The fermentation tests, done with 1 per cent "sugars" either in tryptic broth or in 10 per cent ascitic agar with Andrade's indicator, agreed uniformly. With dextrose, sucrose, lactose and mannite there was growth with acidification ("fermentation"), and in the petrolatum-topped tubes of liquid medium, production of gas. With xylose there was no fermentation or apparent growth, but gas was produced in salicin. A small amount of gas was produced in plain tryptic broth. No growth occurred with plain agar, gelatin, milk or inulin serum. Nitrates were not reduced. Indol was formed both in cooked meat and tryptic broth.

While no final tests were done to determine the viability of the organisms, colonies exposed to air for forty-eight hours contained living organisms. Motility was not demonstrated.

PATHOGENICITY

The virulence of *Act. necrophorus* in man is self-evident from the two cases reported. Rabbits, guinea-pigs and mice were chosen for

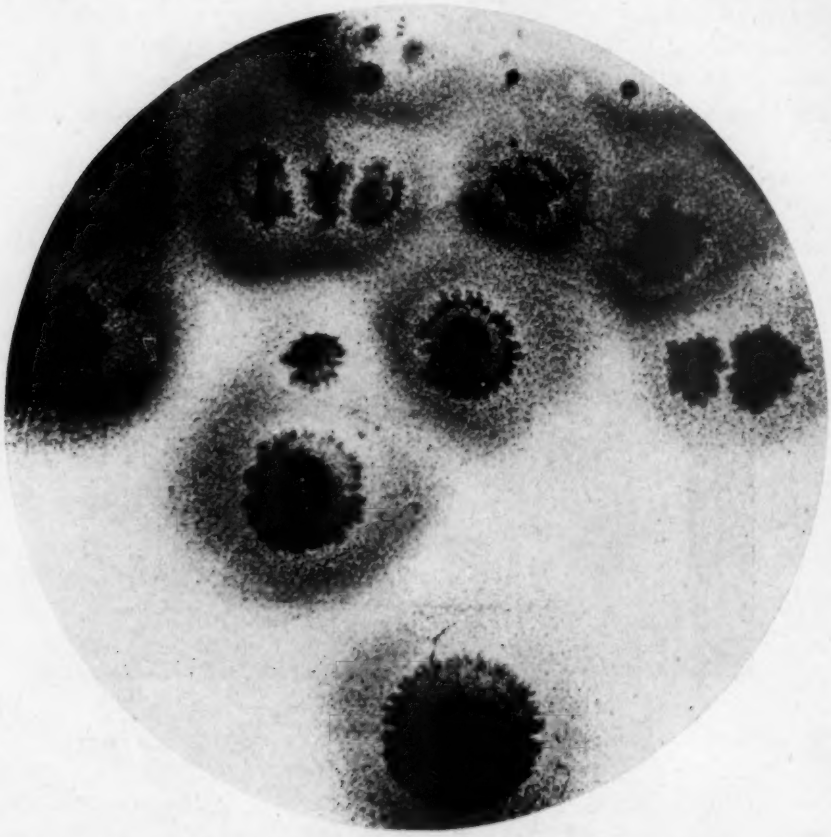

Fig. 7.—Surface colonies of strain A-718 M on a blood agar plate, from seven to eight days old. The dense center, lighter intermediate zone, radial serrations at the peripheral portion of the colonies and the smudging of the hemolyzed area just beyond should be noted.

use in testing the pathogenicity of the organism for animals. Blood taken from the patient in case 1 at necropsy was injected into a guinea-pig the next day (being kept in the cold room over night), 0.5 cc. being injected intraperitoneally. The animal appeared lethargic for several days, but at necropsy, two and a half months later, was normal. Diluted

psoas pus from the same patient was injected, 0.25 cc. intracutaneously, into a guinea-pig. A small hemorrhagic tumor resulted, but this animal also was normal at necropsy, two and a half months later. A guinea-pig inoculated subcutaneously with 0.5 cc. of a seven-day broth culture of strain A-718M developed a local tumor, which rapidly subsided, leaving no evidence of inflammation thirty-seven days later at necropsy. A white mouse into which 0.5 cc. of the same material had been injected intraperitoneally died three days later, weighing one fifth less and having a greenish, fibrinous peritonitis with a foul odor.

Rabbits were susceptible to infection with *Act. necrophorus* (strain A-718M), as table 1 shows. Subcutaneous inoculations (rabbits 88 and 91) were followed by an intense inflammatory process with gangrene,

TABLE 1.—*Pathogenicity of Act. Necrophorus, Seven-Day Broth Culture (Strain A-718M) and Filtrate, for Rabbits*

Rabbit	Weight, Gm.	Inoculation: Location	Inoculation: Amount, Cc.	Weight Loss, Gm.	Lesions in Life	Died or Was Killed	Days	Pathologic Changes at Necropsy
88	2497	Subcutaneous, abdomen	1.0	...	Abscess	Killed	32	None
91	2383	Subcutaneous, ear	0.1	...	Abscess	Killed	32	None
85	3114	Left knee joint	0.2	624	Sick	Killed	24	Necrosis of soft tissues and bone
86	2837	Intravenous	1.0	681	Sick	Died	11	Intercurrent pneumonia (?); early liver abscesses
87	2837	Intravenous	1.0 + 1.0 cc. immune rabbit serum	500	Sick	Died	12	Necrobacillosis of liver
95	3072	Intravenous	2.0	794	Sick	Died	11	Necrobacillosis of liver; jaundice; splenic tumor
89	2383	Intravenous	1.0 (filtrate)	113	....	Killed	32	None
90	2496	Intravenous	1.0 (filtrate) + 1.0 cc. immune rabbit serum	340	Sick	Killed	32	None

formation of abscesses (fig. 8), rupture, sloughing and spontaneous healing. This was most marked following injection into the abdominal wall. Intravenous injection of cultures (rabbits 86, 87 and 95) was followed by progressive loss in weight, profound toxemia and death. Jaundice, delayed clotting of the blood and specific abscesses of the liver were found at necropsy. The injection of filtrate resulted only in a slight immediate and temporary loss in weight. Equal quantities of "immune serum" (table 2) injected simultaneously with cultures and filtrate had no perceptible effect, other than that which might be represented in the greater loss of weight in the animal employed for this experiment than occurred in the rabbit into which filtrate only had been injected. No local injections of filtrate were attempted, nor was the pathogenicity of strains A-650 Bld, A-650L or A-650 Med determined.

Fig. 8.—Large, blackened gangrenous abscess three days after subcutaneous injection of a broth culture of Act. necrophorus A-718 M into a rabbit.

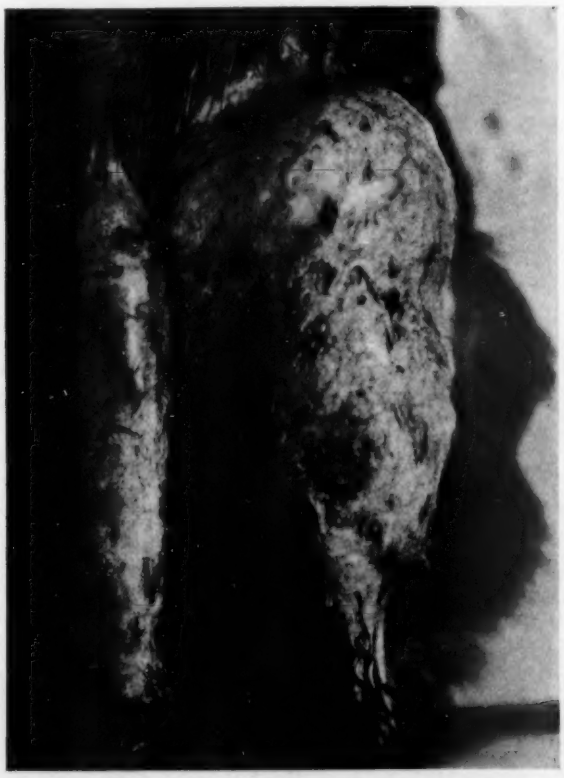

Fig. 9.—Multilocular abscesses resulting from the injection of 0.2 cc. of a culture of Act. necrophorus A-718 M into the left knee joint of a rabbit.

TABLE 2.—*Titration of Agglutinins and Cross-Agglutination in Serum of Rabbits Immunized Against Act. Necrophorus A-650 Bld and A-718 M*

Rabbit	Antigen		Dilutions of Immune Serum									
	Immunization	Agglutination	1:2,560	1:5,120	1:10,240	1:20,480	1:40,960	1:81,920	1:163,840	1:327,680	1:655,360	C
356	A-650 Bld.	A-650 Bld. (case 1)	++++	+++	++	++	+	0	0	0	0	0
356	A-650 Bld.	A-718 M (case 2)	++++	+++	++	0	0	0	0	0	0	0
357	A-650 Bld.	A-650 Bld.	++++	++++	+++	++++	++++	++++	+++	++	+	0
357	A-650 Bld.	A-718 M	++++	+++	+	+	0	0	0	0	0	0
358	A-718 M	A-650 Bld.	++++	+++	+	±	0	0	0	0	0	0
358	A-718 M	A-718 M	++++	++++	+++	+++	++	+	0	0	0	0

The most spectacular production of lesions was obtained on infecting rabbit 85 in the left knee joint. Inflammation, tenderness and limitation of motion resulted, followed by the formation of tremendous multilobulated abcesses of the soft tissue (fig. 9). Weakness and excessive loss of weight were present (table 1). Roentgenograms

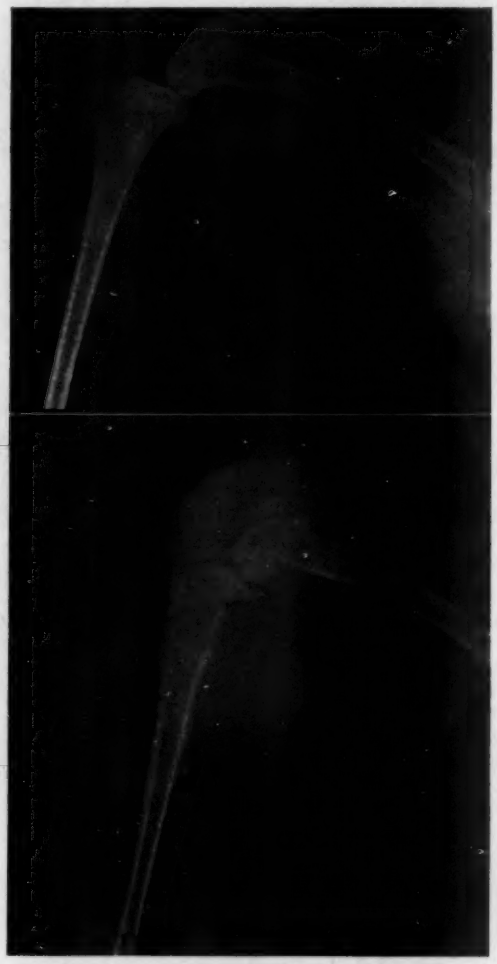

Fig. 10.—Lateral view of right (normal) and left (infected) knee joint region of rabbit. The abscesses of the soft tissues, the destruction of the diaphyseal portion of the bone shafts, and the periostitis following the injection of Act. necrophorus A-718 M should be noted.

showed, in addition to the swelling of the soft tissue, extensive destruction of bone about the diaphyseal ends of the shafts of the femur, tibia and fibula, with advanced proliferative periostitis (fig. 10). No visible

change in the joint surfaces was apparent. At necropsy, the large, nodular, fluctuant swellings incised through edematous, pale, semi-translucent, glassy walls composed of skin, muscle and fascia revealed a large amount of thick, granular pus of a creamy, yellowish appearance. The odor was exactly that of Swiss cheese. All anatomic relationships were lost in the mass of multilobular abscess walls with frayed, fuzzy, stringy strands of pale caseous muscle, fascia and fibrous tissue. The caseous mass was tough and stringy near the walls and thinned in the center. The knee joint was involved, presenting a dirty bluish discoloration and thickening. Intense destruction of bone had occurred in the diaphyseal portions of the femur, tibia and fibula, and the bone-marrow had a washed-out appearance. No gas was discovered. Aerobic and anaerobic cultures of the heart blood and of the contents of the abscess were made. Those of the blood were sterile, and those of the abscess yielded *Act. necrophorus* in pure culture. Microscopic sections of the wall of the abscess and of the synovial membrane showed loss of cellular structure, edema, necrosis, clusters of blue-staining bacteria and considerable eosinophil infiltration; in the spleen there was necrosis with swelling of the splenic centers and eosinophil invasion; and in the kidney, extensive swelling of the tubular epithelium, which had a finely granular, acidophilic cytoplasm.

SEROLOGY

Rabbits were employed in an attempt to obtain agglutinins for *Act. necrophorus*. Two animals each were subjected to injections of strains A-718M and A-650 Bld. Serum taken from the animals before the injections were commenced and tested for agglutinins (in dilutions from 1:20 to 1:2,560) proved negative. The injections were made in periods—four daily inoculations of gradually increasing doses alternating with four days' rest. The antigens were made from three-day anaerobic broth cultures which had been heated to 60 C. for thirty minutes, washed twice in physiologic solution of sodium chloride and concentrated approximately five times. The amount of this antigen was 0.05 cc. at the beginning and 2.2 cc. at the end of the series of injections, thirty three days later. The immune serum was drawn ten days after the last intravenous injection. Attempts to secure blood from rabbit 359 on the same day as from the others was unsuccessful, so that the final agglutination tests were not done with the serum of this animal.

The results are shown in table 2. A high titer of 1:655,000 was obtained with the serum of rabbit 357 when the same antigen strain (A-650 Bld) was used as had been employed in the immunizing injections. Cross-agglutination was apparent, to but slightly lower titers

than those obtained with the homologous antigen. Great difficulty was experienced in securing a suspension of antigen which would not spontaneously agglutinate. After trying various vehicles, the five-day old broth cultures of both strains were successfully suspended in a phosphate buffer with a calculated p_H 7.1,[12] after being washed once in physiologic solution of sodium chloride and concentrated from two to 4 times. Controls consisted of half mixtures of the antigens with physiologic solution of sodium chloride. The tests were done in the water bath at 56 C. for two hours.

COMMENT

Necrobacillosis in man is probably more common than previously has been supposed. Few bacteriologic textbooks mention the organism. Albrecht [3] stated that "undoubted infection in man has not been proven," despite the three cases of cutaneous infection cited in this paper. If anaerobic blood cultures were made more frequently in the case of patients with obscure fevers or with pyogenic focal infections, it is probable that *Act. necrophorus* would be more frequently detected. This is especially applicable in the case of patients exhibiting jaundice, as well as fever, in which the ordinary etiologic agents have not been recognized.

Dr. Lawrence A. Kohn has shown me the interesting record of a colored girl, aged 19, who was under his care in the Strong Memorial Hospital in 1926, in the Medical Service of Dr. William S. McCann.

The patient for several days had suffered with headache, sore throat, chills and fever. On admission she had much enlarged and inflamed tonsils, from which foul green pus exuded; the cervical lymph nodes were enlarged, and the conjunctiva slightly inflamed; the leukocyte count was 30,000, and the fever of an intermittent type, ranging between 38 C. and 41 C. (100.4 to 105.8 F.). The high "spiking" fever persisted; icterus and petechial hemorrhages were detected in the sclera and conjunctiva, and the patient continued to be very ill. The case was a diagnostic puzzle for some time. Throat cultures were negative for *B. diphtheriae* and showed only about 25 per cent hemolytic streptococci. The patient developed empyema in the right side of the thorax. Operative drainage was instituted and "a large amount of gas and thick, foul-smelling, muddy colored pus" was removed. A gram-positive coccus was seen in smears and aerobic cultures of the pus. Two anaerobic cultures of this pleural effusion and four blood cultures yielded a gram-negative bacillus. This organism was small and pleomorphic, growing at times in chains and rods; it possessed a distinctly foul odor; it appeared to be moderately proteolytic; and it produced gas in dextrose and other mediums. Unfortunately, the organism was lost before it could be identified. The patient ultimately recovered.

12. Clark, W. M.: The Determination of Hydrogen Ions, ed. 2, Baltimore, Williams & Wilkins Company, 1922, p. 114.

Dr. Kohn saw the cultures in cases 1 and 2 and felt that there was a strong resemblance between them and those obtained in his case. From the clinical history and the characteristics of the organism recovered in his case, it seems highly probable that the organism was *Act. necrophorus.*

The presence of gas in the cellulitic tissue of the neck in case 2 was recognized clinically and by roentgen examination (fig. 2). In case 1, only indefinite changes were seen in the second roentgenograms of the left sacro-iliac and hip joints (fig. 1). During a careful reexamination of the films in the two cases, the roentgenologist and I found additional evidence of an infection with *Act. necrophorus* in the left hip joint of the patient in case 1, which had escaped notice in the previous examination. A tract of gas medial and anterior to the neck of the femur and lesser trochanter had developed in the soft tissues. In view of the nature of the organism recovered in this case, the presence of gas is readily explained.

In case 1, it is to be noted that the first clinical impressions (the intern's) proved to be nearly correct; the later desperate condition of the patient masked the true picture to the extent of leading to a subsequently erroneous diagnosis.

SUMMARY

An organism having the morphologic, biologic, pathologic and serologic characteristics of *Actinomyces necrophorus* was isolated in two fatal cases in man exhibiting some of the characteristics of infection with this organism in animals. Necropsies further confirmed the resemblance of the lesions to those due to *Act. necrophorus* in animals.

Experimentally, the organism was pathogenic for rabbits and mice, and questionably so for guinea-pigs. In one animal, the lesions of the joint infection as seen in case 1, were reproduced, with additional destructive changes in the bone and soft tissues.

A high titer (1:655,360) of agglutinins was obtained following periodic intravenous injections of the heated, washed, concentrated organisms into rabbits. A correspondingly high degree of cross-agglutination was secured with strains isolated from both cases.

An additional case is noted, of a patient with follicular tonsillitis and empyema with some clinical features similar to those seen in case 1, from whom, in 1926, Dr. Kohn isolated a gram-negative anaerobic, pleomorphic bacillus in the blood and empyema pus. The morphologic, cultural and clinical characteristics of this organism warrants its presumptive classification as *Act. necrophorus.*

CONCLUSIONS

Two cases of necrobacillosis in man, the fourth and fifth instances of proved infection with *Act. necrophorus* in man, the only fatal cases

on record, and cases presenting hitherto undescribed types of human infection, were verified by bacteriologic study.

The organisms obtained in the two cases were shown to be practically identical.

Necrobacillosis is a disease with recognizable clinical features in man. Its potentialities for morbidity and mortality should, therefore, warrant a careful search by physicians for its presence in cases of obscure infection. Anaerobic cultures on a wider scale in the routine laboratory are therefore suggested for detecting *Act. necrophorus* in cases in which human necrobacillosis is suspected.

PRIMARY CARCINOMA OF THE LUNG FOLLOWING TRAUMA *

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In a recent review on the causal relation of trauma to tumors, Knox [1] has emphasized the difficulties in establishing such a relation, without emphasizing the evidence that has so far been presented on the positive side, or the difficulty in disproving the claimed causal relation in any suspected case. The negative side of this argument is certainly the easier one to support. No matter what evidence of relationship of the trauma to the subsequent tumor may be presented, there is no possible way of proving that a symptomless tumor had not already been present at the time and at the site of the injury. But that such a coincidence can account for all the cases in which a tumor has arisen at the site of a single trauma after a time interval compatible with the assumption of cause and effect, is somewhat of a strain on an unprejudiced imagination. Even if many of the cases of supposed development of a tumor as a sequel of a single trauma are reported inadequately to furnish positive proof of the causal relation of the trauma, this defect does not prove that the assumption of traumatic etiology was always incorrectly made.

In view of the lack of satisfactory case reports, it is apparent that more data are needed, and that cases presenting an apparently probable relationship between a single trauma and a subsequent tumor should be placed on record in order that they may receive consideration by future investigators of the problem. Recently, through the kindness of Dr. Ludvig M. Loeb, I have had an opportunity to study a case of primary carcinoma of the lung which falls into this category, and which seems to be of especial value because the roentgen plates of the site of the injury made immediately after the injury was received show that at that time there was no recognizable evidence of malignant growth.

REPORT OF CASE

A man, aged 50, in general good health, was knocked down by an automobile, on Sept. 1, 1926. He suffered severe pain in the chest and was taken to a hospital,

* Submitted for publication, Dec. 3, 1929.

* From the Department of Pathology of the University of Chicago, and the Otho S. A. Sprague Memorial Institute.

1. Knox, Leila C.: Trauma and Tumors, Arch. Path. **7**:274, 1929.

where a roentgen examination the next day revealed fracture of the left third, fourth and fifth ribs in the midaxillary line. There was also distinct evidence of traumatic injury to the lung, namely, hemoptysis and a subcutaneous emphysema extending over the entire body. The roentgen films showed no evidence of any neoplasm in the lung. The fractures healed uneventfully, and the patient seemed to be in good health until the following August, when he began to have pain in the left side of the chest. He developed a cough, and symptoms suggestive of pulmonary tuberculosis appeared, but no tubercle bacilli were found in many specimens of sputum. Repeated bronchoscopic examinations failed to reveal any bronchial growth, but roentgen films now revealed evidence of cancer in the left upper lobe with shadows in the hilum apparently dependent on metastases to the lymph nodes. The clinical course was steadily downward, with evidence of progressive consolidation in the left upper lobe. Death occurred on Aug. 17, 1928, or just one year after the development of symptoms, and just short of two years after the injury to the left lung. The family history revealed that a paternal grandmother died of carcinoma of the breast and that a paternal uncle died of carcinoma of the stomach.

Necropsy.—Necropsy was performed three hours after death by Dr. Paul R. Cannon, and disclosed the presence of a primary carcinoma of the upper lobe of the left lung, with metastases in the mediastinal and left supraclavicular lymph nodes, in the retroperitoneal periaortic lymph nodes as far down as the bifurcation, in the right suprarenal gland and both kidneys. There was a thickening and an irregularity in the third, fourth and fifth left ribs in their middle thirds from the healed fractures. No other changes of significance were found.

Examination of the thoracic contents showed that the left pleural cavity was obliterated by dense fibrous adhesions. The upper lobe of the left lung was found to be almost completely replaced, especially in the upper anterior portion, by a dense white tumor mass. This mass had infiltrated through most of the left upper lobe and diffusely through the mediastinum. There was no tumor growth in the trachea or either primary bronchus, nor in the large branches of the bronchi on either side. The entire tumor mass measured 17 cm. transversely, 11 anteroposteriorly and 15 cm. in the superior-inferior diameter, including the involved mediastinal tissues. In the portions of the upper lobe not involved in the neoplasm, the lung tissue was atelectatic and contained bronchiectatic cavities. Much fluid pus escaped from the smaller bronchi. The left lower lobe was partly compressed and partly filled with air.

The right lung exhibited no tumor nodules or other marked changes beyond hypostatic edema and some emphysematous bullae.

Gross examination indicated that this tumor arose in the periphery of the left upper lobe, rather than in one of the larger bronchi, where primary carcinoma of the lung most usually has its origin.

Histologic Structure of the Tumor.—The tumor was composed of cells which generally appeared elongated, consisting chiefly of nucleus with little cytoplasm, thus much resembling sarcoma cells, but they tended to form alveoli, did not secrete collagen, and often exhibited a palisade arrangement. In no places did the cells exhibit a characteristic epithelial structure, nor did they form tubular structures, secrete mucin, or undergo keratinization. In other words, the structure was that of the type of lung tumors that has often been described in the earlier literature as sarcoma and later as mesothelioma, and which has been interpreted by some as a tumor arising from the flat epithelium of the alveoli. While it is certainly not possible to determine by the histologic character of a pulmonary carci-

noma whether it arose in the bronchi or in the alveoli, or even whether carcinomas ever do arise in the alveoli, the absence of glandlike structures or of mucin, and the tendency to formation of spindle cells resembling a sarcoma, are points that have often been mentioned as in favor of a peripheral origin of a lung carcinoma, or at least as opposed to the origin of such tumors in the mucosa of the large bronchi.

COMMENT

The literature reveals few instances in which a primary pulmonary carcinoma has seemed to result from a single trauma to the lung tissue. Knox,[2] in her review on trauma and tumors, said:

> A serious effort has never been made to ascribe pulmonary tumor to an injury. The case reported by Lepine was that of a man who had sustained an injury to the chest wall and who one year later developed a squamous carcinoma of the lung beneath the site of the old injury. But serious injuries to the chest are so frequent and pulmonary tumors so rare that, statistically, a causal relationship is not even suggested.

Weller,[3] in his recent review on the pathology of lung tumors, said:

> Aufrecht considered severe trauma which "does not produce laceration of the pulmonary tissue, but only molecular disturbances of an unknown character" to be an important immediate cause of pulmonary carcinoma. Four cases which he had seen were preceded by grave trauma. One woman died of carcinoma of the right lung sixteen months after falling from a ladder and striking the right side of the chest. A man accidently received the full weight of a beam, which he was assisting in lifting, on his left shoulder. Two years later he died of diffuse carcinoma of the upper lobe of the left lung. Georgi's blacksmith was hit on the chest by a heavy mass of iron. The third patient described by Scott and Forman had suffered severe contusions of the chest when caught in a belt. The carcinoma, however, developed on the opposite side. In Barron's fifth case, the patient gave a history of a fall from a ladder, striking the chest on a plank, shortly before the onset of pulmonary symptoms. Similar examples are to be found here and there throughout the literature (Hinterstoissen, Handford) but they are so few that one must conclude, contrary to Aufrecht, that a single episode of external mechanical trauma is practically not of importance in determining carcinoma of the lung.

The case herewith reported seems to present as nearly completely satisfactory evidence as one can hope to secure of the development of a primary carcinoma of the lung as a direct result of a single traumatism to the lung tissue. Roentgen plates of the chest made immediately after the injury show that at this time there was no evidence of a carcinoma of the lungs demonstrable by this means. There is conclusive evidence of traumatism to the lung (hemoptysis and severe subcutaneous emphysema). The interval between the time at which the traumatism was received and the appearance of symptoms of the cancer of the lung (eleven months) is entirely in harmony with the assumption that the

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2. Knox (footnote 1, p. 292).

3. Weller, C. V.: Pathology of Primary Carcinoma of the Lung, Arch. Path. **7**:478, 1929.

neoplastic growth was incited by the traumatism of the lung, and the duration of life after this time (twelve months) is in keeping with the rate of growth to be expected from a tumor reaching the observed state in the first eleven months after the traumatism. Finally, the fact that the gross anatomic observations indicate that the tumor began its growth in the periphery of the lung at just the site of the injury, rather than in the large bronchi nearer the hilum where most lung cancers seem to arise, is strong evidence in favor of the hypothesis that this particular cancer resulted from the traumatism to the lung tissue immediately beneath the fractured ribs.

Of course, it is not possible to say that there was not already a carcinoma, too small to be detected in the roentgen film, growing in the part of the lung that was traumatized at the time of the injury. But in view of the extreme infrequency of primary carcinoma of the lung arising in the periphery of the upper lobe, to support such an explanation of this particular case requires a stretching of "the long arm of coincidence" to the vanishing point. There never will be a case of neoplasm following traumatism in which absolute proof can be offered that the traumatism did not occur at a point where a neoplasm had already begun to grow. Absolute proof would have to be furnished by complete serial sections of the tissues at the moment of their injury. Therefore, one must approach the problem of the relation of trauma to tumor with an open mind, keeping in view always the two fundamental but opposing facts.

1. Absolute anatomic proof can never be furnished that a given tumor arising at the site of a trauma has resulted from the tissue damage or subsequent reparative proliferation of previously normal tissues.

2. It is equally impossible to prove that any tumor arising at the site of and subsequent to a trauma is not the result of tissue damage or subsequent reparative proliferation, if there has been no demonstrated tumor at this site at or before the time of the traumatism.

Excessive proliferation of tissue for a considerable period unquestionably leads sometimes to the continuance of the proliferation in the form of malignant growth. There is no known reason why any reparative proliferation, whether of short or long duration, may not assume the malignant character, and hence one must be as willing to accept the principle that a single trauma may lead to malignant growth as that protracted mild traumatism may have the same end-result.

SUMMARY

A case is reported of primary carcinoma of the lung, arising in the periphery of the left upper lobe, at or about the site of a demonstrated traumatism to the lung, which produced hemoptysis and diffuse subcu-

taneous emphysema. Roentgenograms made the day after the traumatism, which showed fracture of the left third, fourth and fifth ribs, gave no evidence of the existence of any neoplastic condition in the lung. Eleven months after the injury pulmonary symptoms appeared, and examination now revealed a neoplasm in the periphery of the left upper lobe at the site of the trauma, which continued to grow until death occurred twenty-three and one-half months after the pulmonary traumatism. The probable relationship of the trauma to the occurrence of the carcinoma in the lung is discussed.

Laboratory Methods and Technical Notes

THE PRESERVATION OF SPECIMENS IN COLOR*

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Until within very recent years but little advance over the technic originally described by Kaiserling has been made in the preservation of gross pathologic specimens in color. The most important of the recent contributions is that of Kerner,[1] who introduced the use of illuminating gas, and who more recently proposed the use of a silicate gel as a mounting medium.

As color changes are among the more characteristic alterations observed in diseased tissues, color retention in specimens which are to be used for teaching or purposes of demonstration is of importance. A method is here presented which has several advantages over the methods now generally in use. This method fixes color better than either the Kaiserling or the Klotz method, calls for but one solution, can be carried through in the light, gives fixation which does not fade and is economical. It is virtually a modification and combination of the methods of Klotz and Kerner.

TECHNIC

The appended formula is for approximately 1 liter of solution.

Potassium sulphate	0.5	Gm.
Potassium nitrate	2.25	Gm.
Sodium chloride	4.5	Gm.
Sodium bicarbonate	9.0	Gm.
Sodium sulphite	11.0	Gm.
Sodium acetate	7.5	Gm.
Chloral hydrate	25.0	Gm.
Solution of formaldehyde, U. S. P.	25.0	cc.
Iso-propylalcohol (technical)	50.0	cc.
Water	1,000.0	cc.

A glass tube which is connected with the illuminating gas supply is passed to the bottom of the container, and the gas permitted to bubble through the mixture slowly for about one hour. If the glass tube is 0.5 cm. in diameter, then one bubble every second is enough gas flow. The gas is then turned off and the container immediately closed with a tightly fitting stopper.

The specimen to be preserved is wiped free of blood débris (it is not washed in water) and placed, preferably hung suspended, in a jar sufficiently large so as not to cause pressure at any point. Approximately ten times the volumes of the specimen is sufficient fixative. While the color is immediately fixed, fixation should not be for less than four days; the specimen may be left in the solution inde-

* Submitted for publication, Jan. 24, 1930.

* From the Achelis Laboratory, Lenox Hill Hospital.

1. Kerner: Centralbl. f. allg. Path. u. path. Anat. **36**:5, 1929.

finitely. It is best, before placing the specimen in the fixing fluid, to prepare it as it is finally to appear, by sewing it to sheet celluloid, which is practically invisible when the specimen is mounted in gelatin.

If mounted in gelatin or a similar gel, then the used fixative is filtered and returned to the original stock. If the stock solution is not used up, gas should be permitted to bubble through it for about thirty minutes once a month; or should that be forgotten, then gas should be introduced for thirty minutes at least two hours before a specimen is placed therein. Specimens left in the fixing fluid do not become hard and stiff.

For mounting in gelatin, the method is as follows: One liter of water is brought to the boiling point, the heat is removed and 100 Gm. of gelatin of exceptional purity is rapidly added in small pieces. The mixtures is stirred until complete solution has occurred and then from 3 to 4 teaspoonfuls of activated charcoal (I have used Darco decolorizing carbon) is added for each 100 cc. of the gelatin. The solution is to be stirred and kept hot for five minutes. It is then filtered through a Beuchner funnel with suction, the mat for the filter being either washed asbestos or a piece of snugly fitting, closely woven cloth, such as linen. The filtrate is refiltered until clear. Coarse filter paper without suction may also be used; but with suction, filtration of one liter takes about five minutes. This gives a gelatin that is water clear and practically colorless. The excess fixative having been permitted to drain off and the specimen having been placed in the chosen jar, 4 cc. of 40 per cent formaldehyde is added to each 100 cc. of melted gelatin, and the jar filled with this mixture. The resultant gel is practically irreversible.

General and Historical Reviews

SICKLE CELL ANEMIA*

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EARLY HISTORY

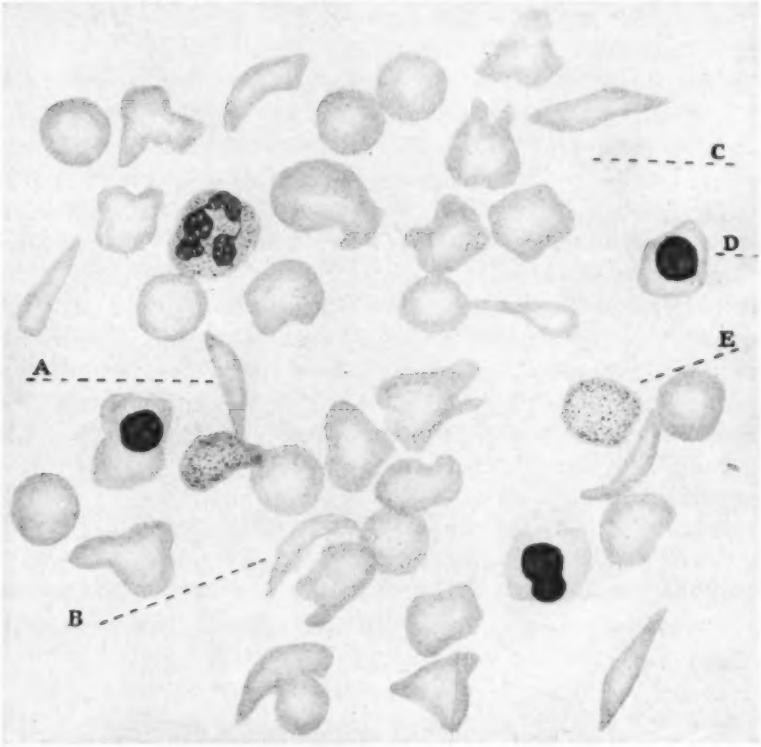
Hayem, in his book on "Blood and Its Anatomical Variations," described semilunar erythrocytes, which he interpreted as artefacts. The next mention in the French literature of this abnormality of the red blood cells was made by Sergent and Sergent, who examined the blood of a large number of natives of Algiers, who are composed of Moors, Berbers, Arabs and negroes. The authors found that 5.1 per cent of 234 malarial native patients had "demilune" erythrocytes. Examination of the blood of 265 nonmalarial natives did not reveal any deformity of the red blood cells. These same authors found demilune red blood cells in the blood of European malarial patients; and they therefore concluded that demilune erythrocytes are characteristic of the blood picture of malaria. Brumpt found demilune erythrocytes not only in the blood of malarial patients, but also in that of persons suffering from various forms of intoxication. Langeran observed similar forms of red blood cells in white rats and guinea-pigs with rickets. The last author reproduced these demilune forms in other guinea-pigs and rats by injecting lead acetate into these animals. Langeran assumed that this experiment supported Brumpt's conception that the demilune erythrocytes are produced by intoxications. It is questionable whether the French writers were dealing with the same deformity of the red blood cells to which the American school gave the name of sickle cell.

In 1904, Dresbach reported the presence of elliptical red blood cells in an apparently healthy young mulatto student, who, examining his own blood smear, noticed these peculiarly shaped erythrocytes which constituted 90 per cent of his red cells. No mention is made, however, of the total number of erythrocytes or the quantity of hemoglobin. Austin Flint took exception to Dresbach's statement that the mulatto was healthy and suggested that the elliptical red blood cells were poikilocytes and that the student had some form of a primary anemia. The following year, Dresbach wrote that the mulatto had had tonsillitis and then an attack of acute inflammatory rheumatism and had died of cardiac

* Submitted for publication, Nov. 21, 1929.

* From the Laboratories and the Department for Medical Research of Toledo Hospital.

failure, but insisted that the symptoms and death had no connection with the elliptical red cells. It remained for Herrick in 1910 to point out in a negro patient the association of the elliptical or sickle-shaped red blood cells with a severe anemia and with certain clinical manifestations, and thus establish a probable new disease entity. There is a strong probability that Dresbach's student had a condition similar to the one Herrick described. Since Herrick's paper, a fairly voluminous literature on the subject has been compiled. In 1922, Mason gave the disease the name of sickle cell anemia, which has been generally accepted.



The blood in sickle cell anemia. *A* indicates an oat-shaped cell; *B*, the sickle cell; *C*, bizarre-shaped cells; *D*, a nucleated red cell, and *E*, a reticulocyte.

INCIDENCE OF SICKLE-SHAPED ERYTHROCYTES

For thirteen years following Herrick's publication, only three additional cases of sickle cell anemia were reported (Washburn; Cook and Meyer; Mason). In the next two years, the interest in the subject was further stimulated by the publications of Sydenstricker and his associates, who demonstrated that sickle cell anemia is not an infrequent disease. Both Huck and Sydenstricker found sickle cells in the blood

of patients' relatives, some of whom presented few or no abnormal clinical manifestations. These observations prompted several routine examinations of the blood of apparently healthy people. Cooley and Lee examined 400 colored patients and found that 30 (7.5 per cent) of them had sickle-shaped erythrocytes but no anemia or disturbing symptoms. In Levy's series of 213 colored people, 12 (5.6 per cent) showed sickle cells and in Graham and McCarty's series of 858 negroes, 58 (6.75 per cent) showed these cells. Of Josephs' 250 colored patients, 16 (6.4 per cent) had sickle red blood cells. Cooley and Lee proposed the term sicklemia for the condition in which sickle red blood cells are present without any other abnormality of the blood or apparent disturbance of health.

Sydenstricker examined the blood of 1,000 white people and was unable to demonstrate the presence of these peculiarly shaped erythrocytes; Miyamoto and Korb examined 100 white patients with similar results. Until Lawrence's publication in 1927, it was generally accepted that the sickling phenomenon was peculiar either to the negro race or those with negro blood. Lawrence found sickle cells in a white woman, her brother, a sister and a niece; and on examination of 102 white people, found sickle cells in the blood of three of them. Lawrence's observation gives a significance to Castana's report (1925) of a case of anemia with the presence of gigantocytes of a semilunar form in a white child. Stewart reported sickle cell anemia in a child whose mother was Cuban without any known negro blood and whose father was white. The probability that this disease is not limited to the negro race is further strengthened by Cooley and Lee's report of sickle cell anemia in a Greek family.

THEORIES OF THE FORMATION OF SICKLE-SHAPED ERYTHROCYTES

Following the recognition of the sickle-shaped erythrocytes, much speculation was aroused regarding their formation and origin. Although Emmel was the first to observe the presence of the sickle forms in the blood of a father and daughter, the conception of the sickle cell trait as familial and hereditary originated with Huck, who had the opportunity to examine members of three generations of one family. Huck found that the sickling trait was transmitted both by the male and the female, the transmission apparently occuring according to Mendel's law for the inheritance of a single factor, the sickle cell condition being the dominant. The observations of Sydenstricker and his associates are in apparent agreement with those of Huck regarding the hereditary and the familial tendencies. Cooley and Lee, however, found that the transmission was through the mother. In a small series of cases, they did not find a single instance in which the father's blood was positive

for sickle cells and the mother's was negative, although the reverse was true. The last workers also concluded that the condition is "congenital, familial and hereditary," but failed to show evidence to substantiate the opinion that sicklemia is a combined congenital and hereditary phenomenon. Sydenstricker observed sickle cells in the blood from the umbilical cord, as well as in the infants whose mothers had sickle-shaped red cells.

Cooley and Lee advanced an interesting hypothesis of a possible African tribe in which the sickle cell is the normal erythrocyte, but this theory is untenable if the finding of sickle cells in the blood of white people is true. That sickling is familial in the sense that it occurs in more than one member of the same family is concurred in by numerous writers on that subject. The sickling trait (sicklemia) is generally accepted as being hereditary. The term hereditary is rather vague. Is it to be understood that the offspring inherits the constitution of either parent with the special defect that allows the formation of sickle cells or that some bacterium is present in the ovum or in the spermatozoon and is responsible for the sickle cell? Or are we to believe that bacteria or their toxic products either affect the ovum or the spermatozoon or pass through the placenta and act on the embryo? The inference drawn from the contributions of various authors is that the idea of an inheritance of a constitution with a special defect is the one that is understood. Huck amplified this view by maintaining that this inherited defect is a dominant character. It appears that the available data in the literature are insufficient for the absolute acceptance of the conception of the sickle cell as hereditary. In order to obviate an accidental coincidence, observations on more than one family are necessary to establish Mendel's law for a given characteristic. If statistical data such as presence of a disease in parents and in their children are to be accepted as conclusively demonstrating an inheritance of a defective constitution, syphilis, if its etiology were unknown, could be explained on similar grounds.

Hahn and Gillespie, in a series of ingenious experiments, concluded that anoxemia is responsible for the formation of sickle-shaped forms in susceptible red blood cells. These investigators observed that on introduction of carbon dioxide, nitrous oxide and nitrogen into the medium containing susceptible erythrocytes, the normal discoid forms assumed a crescent shape, but when to this medium was added oxygen in a concentration of more than 6 per cent (a partial pressure of 45 mm. of mercury) the sickle cells resumed their normal shape. As a corollary, the authors hypothecated that the cause of the change of the susceptible red blood cell resides in the state of the hemoglobin: when the hemoglobin is in a combined state, the discoid erythrocyte is the result; when it is in an uncombined state, the elliptical cell is produced. They

also found that the *p*H changes of the medium (a decreased acidity resulted in an increase of sickle cells) apparently influenced the dissociation of oxyhemoglobin. These important observations demand further experimental corroboration.

Josephs believed that the changes in the surface tension of the cell and the serum with adsorption are responsible for the formation of sickle cells. This conception finds some indirect experimental verification in Hahn and Gillespie's experiments. When a surface of separation is present between a solid and a liquid, the molecules composing the surface are unable to move freely out of the plane and thereby acquire a resistance to rupture and an adaptability to a change of shape made possible by alterations in the interior of the solid. The surface tension of a liquid may be decreased by adding an acid; the protoplasmic gel of the solid will swell and change its contour. Hahn and Gillespie showed that an increased acidity of the medium resulted in the formation of sickle cells; a decreased acidity produced discoid erythrocytes. The last mentioned authors pointed out, however, that the change in the *p*H alone in the medium is insufficient to alter the shape of the cell. It may be assumed either that the gas also contributes to the change of the surface tension or that two factors operate: (1) an alteration of the surface tension and (2) the chemical state of the hemoglobin, as suggested by Hahn and Gillespie.

Emmel suggested that the sickle cell is produced by an accentuation of the normal hematogenetic activity which transforms a spherical erythrocyte into a biconcave disk.

Levy stated that the sickle-shaped erythrocyte is an embryonic normoblast that entered the circulation prematurely and is unable to assume the biconcave form. He based his belief on observations of extruded nuclei, a large number of normoblasts and the division of red cells in the same preparation in which are found sickle-shaped cells. Sydenstricker and Dreyfoos were of the opinion that there is some hereditary defect of the spleen and possibly of blood-forming organs which produces a change in the form of the erythrocyte. Hahn and Gillespie found sickle-shaped red cells several months after splenectomy had been performed (similar results reported by Stewart, Hahn, Bell, Kotte and their co-workers) and deduced from this that the spleen is not responsible for the sickle shape of red blood cells.

The bone-marrow and the general circulation are the two suggested sites of the formation of sickle cells. Sydenstricker believes that sickling occurs in the bone-marrow as a result of faulty erythropoiesis. Emmel, however, showed both in blood cultures and in direct smears various stages of transformation of disk-shaped erythrocytes into sickle shapes and therefore concluded that the change occurs in the circulation. Among others, Wollstein and Kreidel, on the other hand, observed

nucleated sickle cells in the bone-marrow. It is likely that whatever factors operate in changing the form of the red cell, these factors act equally on the erythrocyte in the circulation and in the marrow, and on the mature as well as the immature cell.

CHARACTERISTICS OF SICKLE-SHAPED ERYTHROCYTES

Emmel pointed out that if a culture preparation of the blood of a patient with sickle cell anemia or of a susceptible (sicklemic) person is allowed to stand at room temperature for several hours, most of the normal disk-shaped corpuscles become sickle shaped. These observations were verified by Huck, who noticed that in the blood of susceptible persons, 25 per cent of the normal erythrocytes, on standing for twenty-four hours, became bizarre or sickle-shaped. These observations were repeatedly confirmed by other investigators, and the phenomenon has been referred to as "latent sickling." Cooley and Lee stated that the rapidity of formation and the number of sickle cells in wet preparations have no relation to the presence or the absence of clinical manifestations, as suggested by Huck. Both Graham and Anderson drew attention to the inconstancy of sickle cell formation in wet smears. Smears prepared at the same time and under similar conditions showed either the presence or the absence of sickle forms. Huck found that if a blood culture preparation containing sickle cells was allowed to stand for from three days to six weeks, the cells resumed their spherical form. Levy, on the other hand, observed that sickle cells in wet preparations of blood from persons with sicklemia failed to revert to the normal spherical biconcave disks. The reversal of the sickle cell to a biconcave or spherical form and vice versa was accomplished by Hahn and Gillespie by the introduction of various gases into blood preparations. The experiments of Hahn and Gillespie offer an explanation of the phenomena observed by Emmel and Huck.

The blood preparation usually employed consisted of a hollow slide with an inverted cover slip on which was placed a drop of blood; the cover glass was then rimmed with petrolatum. Such a preparation, probably by exclusion of oxygen, changed the biconcave disks to sickle forms. Hahn and Gillespie traced in vitro the various stages of the change from a biconcave disk to a sickle corpuscle. At first there was a change of refractivity of the erythroplasm; then a blotchy opacity appeared on one side of the rim and extended across the cell in radiating lines. This opaque blotch grew thicker, while the side opposite it became thinner, until it was hardly visible. The opaque side gradually showed a decrease in its curvature, while the thinned out side stretched from horn to horn to a half moon shape, the horns becoming longer and the thin side concave until a crescent was produced. In the light of this description, the

various forms observed by Emmel in stained smears and fresh blood preparations may be accepted as having been the stages in the transformation of a biconcave erythrocyte into a sickle one, and it suggests that sickling, for the greater part, occurs in the circulation.

Sydenstricker and his associates placed blood preparations containing sickle cells in the icebox and found no increase in the number of the sickle-shaped erythrocytes. On the other hand, similar preparations placed in the incubator resulted in a maximum number of sickle cells in four hours. The authors concluded that cold inhibits, while heat accelerates the formation of sickle cells. Apparent contrary results were obtained by Cooley and Lee, who placed a blood preparation containing sickle cells in the incubator (probably at 37 C.) and found that the sickle erythrocytes had disappeared from the blood at the end of twelve hours. The last mentioned authors maintained that the absence of sickle cells was not due to a reversion to biconcave disks, but to a complete hemolysis. Levy confirmed Sydenstricker's observations that cold (0 C.) inhibits the formation of sickle cells, and also expressed the belief that refrigeration acts as a fixative of red blood cells and prevents distortion of form. Levy also observed that incubator temperature (37 C.) accelerated the formation of sickle cells, the change being complete in twenty-four hours. At the end of that time, the sickle erythrocytes began to fragment and many of the fragments were phagocytosed by leukocytes. The contradiction in the results obtained by the investigators in the time necessary for the complete reversion of the spherical cells to sickle cells (Sydenstricker, four hours; Levy, twenty-four hours; Cooley and Lee, complete disappearance of sickle cells in twelve hours) may lie in a difference in the conditions of the patients (sicklemia or sickle cell anemia) or a difference in the quantities of available oxygen in the preparations or some other difference in the experimental conditions. From these various experiments, it may be concluded that a high body temperature accelerates the formation of sickle cells, which are then destroyed by fragmentation.

Huck placed preparations of the red blood cells of people with sicklemia and sickle cell anemia in absolute darkness at room temperature. Sickle and bizarre shapes were formed just as quickly as in the control preparations exposed to the light, but reversion to spherical biconcave disks occurred with greater rapidity.

Josephs observed that susceptible erythrocytes washed and suspended in isotonic saline solutions retained or reverted to their normal spherical shape, but that when plasma or the third saline washings of red cells from normal or susceptible persons were added, sickle cells appeared. Graham and McCarty also failed to find sickling of centrifugated red blood cells which were placed in large volumes of buffered or unbuffered isotonic solutions. Josephs believed that the serum of any person con-

tains a substance which adsorbs on a susceptible erythrocyte and changes the shape to that of a sickle. This hypothetical substance, he believed, is washed off with saline solution. Josephs' observation that serum is essential for the occurrence of sickling is concurred in by Sydenstricker, Mulherin and Houseal. Huck, however, stated that sickling of red cells is not dependent on serum. He placed susceptible red blood cells, washed in isotonic salt solution, in the serum of normal persons and that of persons with sickle cell anemia and found sickle and bizarre forms in the same proportions as in the control preparations. Since Huck did not examine the red cells after washing, but placed them immediately in serum, his results do not justify his conclusions in the light of Josephs' observations. Hahn repeated Josephs' experiments and found that the introduction of carbon dioxide into a preparation containing erythrocytes that had been washed in saline solution resulted in the production of sickle forms. He concluded that sickling of susceptible red blood cells is independent of any substance in serum. Experiments by different investigators conclusively established that normal red blood cells are not changed to sickle forms by serum from patients with sickle cell anemia, as suggested by Emmel.

When tissue of persons dying with sickle cell anemia was fixed in Zenker's fluid, no sickle red cells were apparent. However, when formaldehyde was used as a fixative, sickle-shaped erythrocytes were found in large numbers (Graham). Hahn and Gillespie explained this phenomenon on the basis of the oxidation of Zenker's fluid. There is an increase in available oxygen and a consequent reversion of the sickle cells to the spherical form.

There are conflicting observations regarding the resistance of the sickle or susceptible red blood cells to various strengths of isotonic salt solutions. Some observers state that the resistance is normal (Sydenstricker; Alden; Cooley and Lee; Wollstein and Kreidel); others maintain that there is an increased resistance (Mason; Graham; Hahn; Landon and Lyman), while Huck found that there is a slight decrease. This contradiction may be due to a difference in the temperatures to which the preparations were exposed (Emmel; Huck; Cooley and Lee; Levy) and also probably to a difference in the condition of the patients. Mason was the only investigator to have made differential counts of the discoid and the sickle-shaped unhemolyzed red cells remaining in the tubes with the varying strengths of isotonic saline solutions to determine the difference in resistance between the sickle and the normal red cells.

Sydenstricker observed in vitro auto-agglutination of red blood cells from patients with sickle cell anemia. This phenomenon was corroborated by Josephs, who found agglutination in washed blood containing sickle cells. This tendency to agglutination was overcome only on

repeated washings of the blood preparation. Hahn also noticed agglutinated red blood cells in sections of the spleen, and I have observed this phenomenon in the lung, kidney and spleen (unpublished).

The fate of the sickle-shaped erythrocyte in vitro under favorable conditions is a reversion to the normal biconclave form. In the presence of adverse influences, the sickle cell is destroyed. This destruction is carried on probably by more than one factor. Emmel pointed out that sickle cells are phagocytosed by large monouclears. This observation was repeatedly confirmed by other investigators. Both Sydenstricker and Lawrence noticed that polymorphonuclears perform a similar function. In addition to the circulating cellular elements, the fixed tissue cells have also been implicated. Jaffé, Wollstein and Kreidel and others observed sickle erythrocytes within the Kupffer cells of the liver, and it is probable that the reticulo-endothelial system as a whole acts in a manner similar to that of the large mononuclears and polymorphonuclears.

Sydenstricker suggested that hemolysis plays a rôle. The practically constant finding of biliary pigments in the blood of patients with sickle cell anemia he believed lends support to the conception. On the basis of an extreme hemolytic activity evidenced by an extract of the spleen from a patient with sickle cell anemia, Sydenstricker intimated that the hemolysis is due to some substance secreted by the abnormal spleen. In-vitro experiments of Levy indicate that fragmentation of sickle cells may occur with consequent phagocytosis of some fragments and possible hemolysis of others.

The spleen as a hemoclastic organ undoubtedly plays a part in the destruction of red cells. There is sufficient evidence to assume that the sickle erythrocyte is considered by the organism an abnormal cell and as such destroyed by the body defenses, of which the spleen is a part.

RELATIONSHIP OF SICKLE ERYTHROCYTES TO SICKLE CELL ANEMIA

A most plausible hypothesis advanced to explain the relationship between the sickle red blood cells and the severe anemia with the presence of similarly shaped erythrocytes is that of Hahn and Gillespie. These authors suggested that the presence of a cardiac or pulmonary disease reduces the oxygen tension, and that as a result the red blood cells of susceptible persons assume the sickle form. As pointed out, the sickle cells, being abnormal, are acted on by the phagocytic and the hemolytic body agents, with a consequent resultant anemia. An almost constant observation at autopsies on persons with sickle cell anemia is an abnormal cardiac condition and less frequently some pulmonary disease. The presence of heart and lung disease would support Hahn and Gillespie's view, if it were possible to exclude these conditions as results or manifestations of sickle cell anemia. Dolgopol and

Stitt submit evidence contradictory to Hahn and Gillespie's view. Of seventy-seven tuberculous negroes, 5.2 per cent had sickleemia in contradistinction to 6.5 per cent of the nontuberculous negroes. Dolgopol and Stitt concluded that anoxemia caused by disease or compression of the lung is not an etiologic factor in the development of sickle cell anemia in sicklemic persons.

Cooley and Lee considered sickle cell anemia a form of familial hemolytic jaundice with a chronic hemolysis of vulnerable red blood cells by some hemolytic agent. In support of this opinion, it has been suggested that the spleen contains a hemolytic substance (Sydenstricker) which acts on sickle cells, but this conception fails to account for the transformation of the normal red blood cells to vulnerable sickle forms.

CONFUSION OF SICKLEMIA AND LATENT AND ACTIVE SICKLE CELL ANEMIA

A good deal of confusion is arising from the introduction of new terms by various authors. Cooley and Lee proposed for the phenomenon of the sickle cell trait the name of sicklemia, which is descriptive and simple. The terms drepanocytemia (Hahn and Gillespie) and meniscocytosis (Mason) are cumbersome and unnecessarily long. Latent sickle cell anemia, as suggested by Sydenstricker, has been erroneously applied to persons with the sickle cell trait, but the term as employed by its originator refers to an entirely different phase of the disease. Sicklemia (sickle cell trait) should be reserved only for those persons whose blood preparations on standing for from several to twenty-four hours show sickle erythrocytes, while the health of these persons is apparently normal, their blood without any other abnormalities and their previous history free of symptoms and signs of sickle cell anemia. Levy erroneously used the term sicklemia for the "symptom complex" that accompanies sickle red cells (Levy's cases included both active and latent sickle cell anemia).

Sickle cell anemia presents two phases depending on the degree of the clinical manifestations and the blood picture. One group of patients shows at the time of examination indefinite blood changes and only a few symptoms and physical signs, but gives a history which may include many or all of the manifestations of the so-called active sickle cell anemia. This group's blood preparations on standing reveal many sickle and bizarre forms. Sydenstricker applies to this phase of the disease the term "latent sickle cell anemia." Another group has marked and distinct clinical symptoms and signs and a definite blood picture. Sydenstricker suggested the name of "active sickle cell anemia" for the condition of this group. It has been observed that patients with an active sickle cell anemia have marked remissions with periods of comparatively good health and sudden recrudescences (Stewart). It is prob-

able that the latent phase represents merely the disease in a stage of remission.

That sicklemia and latent sickle anemia are two distinct phases is further corroborated by necropsies. Sicklemic persons (Cooley and Lee performed necropsies on four) show no pathologic changes suggestive of sickle cell anemia. On the other hand, Sydenstricker found in persons with latent sickle cell anemia dying from some other disease changes similar to, if not of the same degree as, those found in patients with the active form of the disease. Sydenstricker's observations at necropsies also support the idea that the latent phase is the stage of remission, the person dying of some other disease before repeated attacks of the anemia produced the marked changes characteristic of the active disease.

SICKLE CELL ANEMIA

Incidence, Race, Age, Sex, Symptoms and Signs.—Cases of sickle cell anemia have been reported from widely separated localities in the eastern, western and southern parts of the United States. There was one case in Sudan (Archibald), one in Cuba (Stewart) and a questionable case in Italy (Castana). Herrick's patient was a native of the West Indies.

Except for a few instances (the Greek family of Cooley and Lee, Stewart's Cuban child and Castana's patient with the questionable case), sickle cell anemia has been thus far found only in negroes or in those of negro blood.

The disease occurs frequently in children, but it has been observed in persons of all ages, the oldest patient being 78. Since sickle cell anemia probably affects only those with the sickle cell trait (sicklemia), which is believed to be present at birth, the persons possessing this trait are probably exposed to repeated attacks of the disease from infancy. The condition, however, may not be diagnosed until adult life is reached, and if the person afflicted survives the attacks, not until old age. Males are more frequently affected than females in the ratio of 3 to 1.

Most of the essential symptoms and signs of active sickle cell anemia were described by Herrick in his original communication. Herrick's patient had dyspena, cough, palpitation, dizziness, chills, low fever, weakness, an ulcer of the leg, general adenopathy, yellow sclerae and a systolic murmur at the apex of the heart. Descriptions of other cases confirmed the presence of these signs and symptoms in a large number of the patients with sickle cell anemia. Additional manifestations reported by others consist of attacks of abdominal pains with nausea and vomiting, night sweats, headaches, pains of joints and muscles, enlargement of the liver and the spleen early in the disease, cardiac hypertrophy, an accentuation of the second pulmonic sound, a systolic

heart murmur heard best over the pulmonic area, edema of the legs, jaundice, swellings of joints, and a comparatively low blood pressure (average of 105 systolic and 65 diastolic).

The latent phase of the disease manifests itself in pains of the muscles and joints, attacks of abdominal pains, occasionally with vomiting, weakness, dyspnea, green-yellow sclerae, general adenopathy, ulcer of the leg and enlargement of the liver and the spleen (Sydenstricker). It is apparent that the manifestations of Sydenstricker's latent phase vary only in degree from those of the so-called active stage of sickle cell anemia.

Urine and Blood.—The urine reveals frequently a low specific gravity (an average of 1.010), a small amount of albumin and varying amounts of urobilin; hyalin and granular casts are often found, and Graham reported a fixation of specific gravity. The phenolsulphonphthalein output is not appreciably reduced (from 30 to 50 per cent in two hours).

The chemical constituents of the blood, both organic and inorganic, of persons with sickle cell anemia show little or no variations from the normal, except for an increased bilirubin content and the almost constant presence of a positive indirect van den Bergh reaction. In addition, Graham and McCarty observed a variation in the blood cholesterol in different persons of from 208 to 877 mg. per hundred cubic centimeters (by the method of Bloor).

The sedimentation rate of the red blood cells is increased (Graham and McCarty). The bleeding and the clotting time are normal. The number of platelets is either normal or moderately increased (Graham; Sydenstricker; Huck; Bell and co-workers, and others).

The total number of leukocytes in the peripheral circulation varies in the same and in different persons, but is practically constantly increased (from 11,000 to 64,000 per cubic millimeter of blood). The degree of leukocytosis apparently has no relation to the severity of the anemia or of the clinical condition. The leukocytosis may be a manifestation of sickle cell anemia or of some intercurrent disease to which the anemia is believed to predispose the patient (Graham and McCarty), or it may be due to the primary cardiac or pulmonary disease (Hahn and Gillespie) on which the anemia is assumed to be engrafted. Examination of the protocols of autopsies reveals that the associated disease in more than half of the cases may account for an increased number of leukocytes. On the other hand, a common observation in sickle cell anemia is a cellular hyperplasia of the bone-marrow. It is more than probable that the leukocytosis is a manifestation of sickle cell anemia and not of an intercurrent or primary disease. Except for a somewhat larger than usual absolute number of large mononuclear cells (Huck

observed 19.3 per cent in one case), the relative ratio of the constituent types of white blood cells is not disturbed. The relative number of the large mononuclear leukocytes does not seem to bear any relation to the degree of anemia. Occasionally, earlier forms of the granulocytic series (myeloblasts) are found in small numbers (from 1 to 7 per cent).

The amount of hemoglobin and the number of red blood cells in active sickle cell anemia vary, but are constantly moderately or greatly decreased. The relationship between the hemoglobin value and the erythrocyte count is also variable with a consequent shifting of the color index from below 1 (0.45) to 1 or over (1.4). The lowest hemoglobin content observed was 20 per cent (Bell and co-workers), the average being 44 per cent. The smallest number of red blood cells was found by Bell and his co-workers in their patient (976,000 per cubic millimeter); the approximate average is 2,100,000. In latent sickle cell anemia there may be either a normal or a slightly reduced amount of hemoglobin and number of erythrocytes.

In the active phase of the anemia, the abnormal morphology of the red blood cells is marked. There is a moderate grade of polychromatophilia; a marked anisocytosis with a large number of microcytes, fragmentary forms and a few macrocytes; an extensive bizarre poikilocytosis in addition to sickle and oat-shaped red blood cells (from 3 to 100 per cent in direct smear or in blood preparation after several hours); many embryonal forms, consisting mostly of normoblasts with a rare megaloblast; a reticulocyte count of from 10 to 40 per cent, and an occasional moderate punctate basophilia. In the latent stage of the disease, the abnormal morphology is slight or moderate. The direct smear reveals some polychromatophilia, a constant moderate anisocytosis of microcytes, some normoblasts, an increased reticulocyte count and poikilocytosis with sickle-shaped cells in a sealed preparation which has stood for from eighteen to twenty-four hours (Sydenstricker).

PATHOLOGY OF SICKLE CELL ANEMIA

The pathologic material on sickle cell anemia consists of sixteen more or less complete protocols of postmortem examinations. Of the sixteen patients, ten died of some intercurrent disease (three of tuberculosis, two of bronchopneumonia, two of peritonitis, one of meningeal hemorrhage, one of nephritis and one of pyelonephritis), which had no apparent relation to sickle cell anemia. In two other cases, the cause of death is not given, and the published records are too incomplete for one to arrive at a diagnosis. The postmortem protocols of the remaining four patients (one of Sydenstricker, Mulherin and Houseal and three of Wollstein and Kreidel) do not reveal pathologic changes of intercurrent diseases that may account for the deaths. Wollstein and Kreidel assumed that death in their three patients was due entirely to sickle cell

anemia. Certain visceral alterations in the sixteen patients dying from different conditions were so constant that these changes may be considered peculiar to sickle cell anemia. In the consideration of the spleen, additional data are available in the descriptions of the spleen removed at operation as a therapeutic measure.

Ulcers of the Leg.—Single or multiple ulcers of the leg were commonly present in the patients with sickle cell anemia. The ulcers varied in diameter from 1.5 cm. to 7 cm., were oval but more frequently round, and shallow, had a punched out appearance, were slightly undermined and were indurated. These ulcers persisted for a long period of time, but eventually healed with permanent scarring; they sometimes reappeared in the same or another part of the leg either spontaneously or following some trauma. Microscopically, there was a moderate increase of connective tissue in the corium with a diffuse mononuclear (plasma, large mononuclear and some lymphoid cell) infiltration with a sprinkling of neutrophilic polymorphonuclears. In places, blood vessels were surrounded by mononuclear cells. The epithelium stopped abruptly at the edge of the ulcer. The base consisted of granulation tissue (Huck). The scar was glossy, smooth and without pigment, but was surrounded by pigmented skin.

Heart.—The heart was frequently hypertrophied, the hypertrophy being of a moderate degree and confined to the left side, predominately to the left ventricular wall (Hein, McCalla and Thorne, Sydenstricker, Mulherin and Houseal, and others). No abnormalities of the pericardium or the endocardium, either mural or valvular, were found, except in my patient in whom a chronic verrucose endocarditis of the mitral and aortic leaflets was present. The myocardium, however, was frequently observed to have a slight to moderate patchy fatty degeneration (Wollstein and Kreidel; Graham; Hein, McCalla and Thorne). The myocardium of my patient showed a mononuclear infiltration and a patchy muscle necrosis. Both the valvular and the myocardial lesions in my patient are considered to be of rheumatic origin. In the absence of anatomic distortions of the valves, the heart murmurs noted by the clinicians must be assumed to have been functional.

Lungs.—Since no mention is made of any pathologic changes in the lungs in a comparatively large number of the protocols of the postmortem examinations, it may be assumed either that the lungs were normal or that no examination of that organ was made. Five of the patients had either bronchopneumonia or tuberculosis with pulmonary involvement, and whatever changes may have been due to sickle cell anemia were probably obscured. Of the remaining patients there are five (including my patient), descriptions of whose lungs appear in the necropsy reports. Marked congestion of the capillaries and the larger

vessels and the presence of serum in some alveoli were constant observations in all these lungs (the heart was of normal size in three of the five). When the tissue was fixed in formaldehyde, many of the erythrocytes in the blood vessels were sickle shaped. In my patient, the small and the medium-sized pulmonary vessels contained fresh or organized blood thrombi with an occasional one canalized, and as a consequence there were fresh and old infarcts. The cause of the thrombosis may have been either the abnormal and weakened myocardium or the tendency of the sickle-shaped red blood cells to agglutinate. Wollstein and Kreidel described the observation in one of their patients of "wedge-shaped areas of organized pneumonia" and fibrous plugs in some of the alveoli.

Spleen.—The spleen was either enlarged or atrophied. Wollstein and Kreidel correlated the size of the spleen with the age of the patient in a number of cases reported in the literature and found that the organ varied in size but enlarged with exacerbations of the anemia in the first four years of life, while in the older patients the spleen became smaller. Stewart observed the size of the spleen at various intervals in a child from the age of 16 months to that of 5 years. The first attack of sickle cell anemia was probably at the age of 10 months (patient reported to have been sick for 6 months). At the first examination, the organ extended 5.5 cm. below the costal margin; ten months later, it extended 6 cm. below the costal marin; at the age of 4, the spleen was not palpable, and at 5 splenectomy was done and the organ was found to be reduced in size. Stewart noticed that during a remission the spleen became smaller. That the size of the spleen has no relation to the age of the patient per se is apparent from Sydenstricker's three "latent cases" in patients aged 78, 72 and 32 with spleens weighing, respectively, 460, 110 and 280 Gm. It is probable that the severity and the frequency of the exacerbations are the responsible factors. During the first attacks of sickle cell anemia, the organ increases in size; then with repeated attacks the spleen becomes atrophic.

The spleen in the state of enlargement was reported (Landon and Lyman) in one instance to have attained a weight of 621 Gm. (the patient was 4 years old). The enlarged organ was firm and frequently nodular, the cut surface was deep or purple red, the follicles were diminished in size, and the capsule and trabeculae were usually increased in thickness. Histologically, the malpighian bodies were small, and the germinal centers were either absent or showed nuclear fragmentation. Surrounding the follicles were areas of fibrous connective tissue or occasionally pools of blood. The pulp and the sinuses were engorged with red blood cells, the greater number of which were sickle shaped (formaldehyde fixation). The nodules apparent on the external surface

were due to dilated and engorged sinuses. Foot (in the case of Bell and his co-workers) observed a marked increase in the reticulin fibers, which were, however, absent near the malpighian bodies. Rich, on the other hand, did not find any abnormality in the reticulum. A brown pigment giving a positive reaction to the iron stain was found by some (Wollstein and Kreidel; Hahn and Gillespie) within endothelial leukocytes and in the thickened trabeculae. The pulp cells were diminished in number and were crowded by the masses of blood.

The smallest weight of the atrophic spleen was 2.4 Gm. (my patient). The changes in the organ varied in degree with the extent of the atrophy. The external surface was frequently nodular. The cut surface varied from a dark purple to a brown-red; the follicles were small in the moderately atrophic spleen, and absent in advanced atrophy; the capsule and the trabeculae were thickened; there was a diminution in the amount of pulp with the presence of patches of connective tissue. The blood vessels were prominent, and the walls were thickened. Microscopically, the malpighian bodies either were not visible or consisted of a small nest of lymphoid cells without any germinal centers. Scattered throughout the organ were small accumulations of lymphocytes. The follicular remnants sometimes were surrounded by old or fresh hemorrhages or connective tissue. The capsule and the trabeculae were markedly thickened, and there were areas of connective tissue between the trabeculae. In the intertrabecular spaces there was a large amount of blood and brown pigment. The sinuses were always dilated, but sometimes were empty or contained from moderate to large masses of blood. The brown pigment within endothelial leukocytes, in the pulp, in the trabeculae and in the vessel walls not infrequently gave a positive reaction to the iron stain. In a far advanced atrophy there was hyalinization and deposition of calcium in the arterial walls, in the thickened trabeculae and in the connective tissue. Although the splenic artery was never found thrombosed, the lumina of the small and the medium-size vessels were partly obliterated and occasionally contained thrombi. Foreign body cells with phagocytosed brown pigment were sometimes found.

Rich in a review of recent and old autopsies examined seventy-one spleens and stated that the histologic changes of the spleen in "latent and active" sickle cell anemia are sufficiently characteristic to establish a diagnosis of sickle cell anemia from an examination of that organ alone. Rich found an abnormal development of the follicular capillaries and a malformation of the sinuses around the follicles with presence of pools of blood in the pulp about the malpighian bodies. He believed that these abnormalities were congenital and were due to imperfections in the ampullae of Thoma. Hahn and Gillespie were of the opinion that the spleen injures itself when called on, in its rôle of a hemoclastic organ,

to destroy an excessive number of erythrocytes. This splenic overfunction results in congestion, fibrosis and eventually atrophy of the spleen. Rich's observations are vague (no description of the abnormalities is given) and thus far remain unconfirmed. The changes he observed may have been results of splenic overfunction and not necessarily congenital.

Liver.—The liver was consistently moderately enlarged. The architecture of the cut surface was blurred, and the color varied from red to brown. The organ was soft and friable, and in advanced cases of sickle cell anemia there was connective tissue in the central and paracentral lobular zones, as well as an increase in the periportal connective tissue. Histologically, there was an infiltration of round cells in the periportal spaces and not infrequently in the liver lobules. The liver cells sometimes had a granular cytoplasm, and sometimes were atrophied or contained fat globules and a brown iron-containing pigment. The sinusoids were distended, filled with varying amounts of blood, and the lining endothelial cells frequently contained brown granules. The Kupffer cells were large and many contained erythrocytes and iron-bearing brown pigment.

Kidneys.—The kidneys were of normal size or slightly larger. In the greater number of cases, the external surface was finely and irregularly scarred with an occasional large scar. The glomeruli were large and red. The cortical striations were frequently distinct and parallel. The medulla was yellow-green. Histologically, there was an uneven capsular line due to numerous depressions (Sydenstricker, Mulherin and Houseal) and areas of radial scarring with partial or complete glomerular fibrosis and tubular atrophy (Graham). The glomeruli were prominent and the capillaries distended with blood. The tubular system, especially the loops of Henle, the convoluted and the collecting tubules, had large lumina, frequently containing casts; the cytoplasm of the lining epithelial cells was granular and contained yellow or brown pigment (Graham and Wollstein and Kreidel demonstrated a positive iron reaction in the pigment, while Sydenstricker was unable to do so).

Bone and Marrow.—Graham gave the most comprehensive description of the changes in the bone. He observed sclerosis of the cortex and the marrow cavity at both ends with a central red marrow beneath the ulcer of the leg. Elsewhere in the long bones (femur and tibia), the inner half of a generally thickened cortex contained islands of red hyperplastic marrow and areas of necrosis and intramembraneous bone repair. Practically similar changes were observed by Cooley, Witwer and Lee in the bones of the skull and the ribs. The last mentioned authors called attention to the porous appearance of the bones in roentgenograms early in the disease and a pronounced striation in the terminal

stages due to what they believed to be a replacement of the exhausted marrow by new bone. Practically throughout the cortex, Graham noticed lymphocytic foci and endothelial leukocytes with phagocytosed golden-yellow pigment, some of which was free in the form of threads. The marrow of the long and flat bones (Graham, Cooley, Witwer and Lee) consisted of a closely crowded mass of cells including myeloblasts, myelocytes, polymorphonuclears, many of which contained eosinophilic granules, a large number of nucleated red cells in the intercapillary spaces and a larger than normal number of megakaryocytes. Bizarre and sickle-shaped red cells both with and without nuclei were found by other observers (Sydenstricker; Wollstein and Kreidel; Mulherin and Houseal). The reticulo-endothelial cells (Graham) and the large mononuclears (Sydenstricker) contained pigment which varied from a golden yellow to a brown black. Sydenstricker was unable to demonstrate the presence of iron in this pigment, which he also found in intracellular form.

Other Organs.—The mucosa of the stomach and the ileum contained a small number of neutrophilic polymorphonuclears, and the germinal centers of the Peyer's patches in the ileum had a few phagocytic endothelial leukocytes and polymorphonoclears (Graham).

The acinar and the "islet" cells of the pancreas contained a considerable amount of fat droplets. There was also a slight polymorphonuclear infiltration of the acinar epithelial cells (Graham).

The lymph nodes were frequently enlarged owing to a diffuse hyperplasia of the lymphoid cells. There were also some myeloblasts with neutrophilic and eosinophilic cytoplasmic granules, large mononuclears with phagocytosed pigment and a small number of polymorphonuclears in the sinuses and in the parenchyma.

No abnormal changes were observed in any of the other organs.

Bacteriology.—Graham found a hemolytic streptococcus in the heart's blood, but the patient had a bronchopenumonia with an early empyema, and apparently a similar organism was recovered from the lungs. Hahn and Gillespie isolated a green-producing streptococcus from the spleen of a 4 year old child who may have had some pulmonary disease (the authors described signs of impaired lung resonance, moist râles and a friction rub). Wollstein and Kreidel found a *Staphylococcus citreus* and a hemolytic streptococcus in the bronchial secretions of a patient who, however, had a "chronic pneumonia." I recovered from the bone marrow in my patient a pleomorphic gram-positive curved bacillus with the morphologic characteristics of a corynebacterium. The patient probably had a rheumatic lesion of the heart.

Since there is much probable evidence that points to the conception that some disease, possibly cardiac or pulmonary, when affecting a

person with the sickle cell trait, results in an exacerbation of sickle cell anemia, the bacteria found may be assumed to be associated with the intercurrent disease. Graham suggested that the streptococcus may be the responsible agent which acts on a person with an underlying sickle cell trait with a resulting production of sickle cell anemia. It may be also assumed that some micro-organism with a predilection for the bone-marrow produces a chronic inflammatory condition of the cortex (as described by Graham) and affects the marrow erythropoietic and leukopoietic activities and the morphologic appearance of the red cells. This micro-organism may be transmitted from the parent to the offspring and may have a greater pathogenicity for the colored than for the white race.

TREATMENT

Splenectomy, liver diet and blood transfusions are the three outstanding methods of treatment of sickle cell anemia. Sydenstricker suggested the removal of the spleen as a therapeutic measure, and Hahn and Gillespie performed the first splenectomy. Since then, Cooley, Bell, Landon and Lyman, Stewart and Hahn repeated this form of treatment in their cases. The spleens removed were of the atrophic and the enlarged type. In Hahn and Gillespie's patient, four weeks after splenectomy, the total number of red blood cells increased from 1,936,000 to 4,432,000, but the hemoglobin only showed a change of from 30 to 40 per cent. Both in Cooley's and in Bell's cases, there was an immediate rise in the number of red cells, but within six months after the removal of the spleen the hemoglobin and the red cells decreased to the preoperative level. The sickle-shaped cells persisted, and there was a marked increase in the number of the nucleated red blood cells. The white blood cell counts remained persistently high. Symptomatic improvement was reported (Hahn and Gillespie; Landon and Lyman). It is apparent that splenectomy is of questionable and at best only of temporary value in the treatment of sickle cell anemia.

Blood transfusions result in a temporary increase in the number of red blood cells and only in a slight elevation of the hemoglobin value. Cooley, Witwer and Lee found an excessive amount of iron excreted in the urine following transfusion and concluded that the donor's red blood cells were hemolyzed, although the recipient's serum failed to produce hemolysis in vitro. Following transfusion there was a marked increase in the number of normoblasts and megaloblasts, but the sickle forms persisted (Landon and Lyman). Similar to splenectomy, blood transfusions only temporarily decreased the anemia, and failed to stop the hemolytic process and had no effect on the formation of sickle-shaped red blood cells.

Levy fed liver to three patients with sickle cell anemia. In all of them, he found an increase in the amount of hemoglobin and number of red blood cells; in one patient sickling of red cells disappeared; in the other two, the tendency to the formation of sickle cells was diminished. Levy's favorable report demands further corroboration by other investigators.

PROGNOSIS

Persons with the sickle cell trait (sicklemia) have lived to old age without any apparent disturbance in health. The prevailing conception is that sickle cell anemia per se is not fatal. There are only a few exceptions in which no other anatomic cause of death except the anemia was found (Sydenstricker; Wollstein and Kreidel). The patient with sickle cell anemia is subject to periods of indisposition, but recovery follows. It is believed that the disease in a child is more serious (Sydenstricker). The approximate average age in a number of cases collected from the literature at which the patient was first seen by the physician is 23. A patient with sickle cell anemia and some intercurrent disease is more apt to succumb to the secondary condition.

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THE FIRST TEXT OF PATHOLOGY PUBLISHED IN AMERICA

THE "TREATISE ON PATHOLOGICAL ANATOMY" BY WILLIAM EDMONDS HORNER, 1829 *

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The year 1929, which commemorates the founding of the Chicago Pathological Society fifty years ago, marks another anniversary in the history of American pathology, the centennial of the first textbook expressly devoted to pathologic anatomy in this country. The author was William Edmonds Horner, adjunct professor of anatomy in the University of Pennsylvania. It was published by Carey, Lea and Carey, the publishers of the *American Journal of the Medical Sciences,* in Philadelphia in the summer of 1829.

Horner was a native of Virginia, born in Warrenton, June 3, 1793. Well written accounts of his life appear in the several standard works devoted to the biography of American physicians, and Middleton contributed an excellent character analysis to the *Annals of Medical History* (1923). As a boy, Horner was slender and delicate, and he never came to enjoy robust health. He began the study of medicine at the age of 16, as an apprentice in the customary manner of the period. His preceptor was Dr. John Spence, a Scotch physician from Edinburgh, who had settled in Virginia, where he came into special prominence as one of the first and most forceful in introducing smallpox vaccination in this country. Spence was a pupil of the great Scottish physicians Cullen and Monroe, and one who never swerved from the narrow path of Scottish medical doctrine. He died in 1829, the year of the publication of Horner's book on pathology, with which he must have had little sympathy, as I shall bring out later. Horner wrote an obituary, full of regard, in the *American Journal of the Medical Sciences,* of which they were both collaborating editors.

In the natural course of events, Horner went to the University of Pennsylvania to complete his medical studies. The relation of the Philadelphia school of medicine to the Edinburgh school has been well pictured by Dr. J. Gordon Wilson in his presidential address before

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the Institute of Medicine. The leading teachers in the early period had all been graduates of the Scotch school. John Morgan, the founder, had trained with the Scotch William and John Hunter in London and gone to Edinburgh to graduate. William Shippen, Jr., the first teacher of anatomy, had done likewise. Benjamin Rush graduated in Edinburgh after training with Shippen. In Horner's time, the Edinburgh graduates were still in the major positions. Even had Philadelphia not been convenient in location, the Scotch John Spence would certainly have directed Horner there for didactic work to supplement the practical office and bedside experience of a physician's apprentice in a small Virginia city.

Horner's first studies in Philadelphia were cut short by the war of 1812. He entered the army as a surgeon's mate in July, 1813, at the age of 20, and saw much active experience on the Niagara frontier, which he described years later in a series of interesting articles, extracted from his diary.

During a furlough in the winter of 1813-1814, he returned to Philadelphia and graduated, using his recent experience for a thesis on gunshot wounds. Following his discharge from the army, he practiced medicine for a short time in his native town of Warrenton, but after a few months made up his mind to return to Philadelphia. From the outset of his medical training, he had been most strongly attracted to the study of the structure of the human body. In 1815 and 1816 he attended lectures in this subject, where his zeal came to the notice of the great Philadelphia anatomist Caspar Wistar, professor of anatomy. In March, 1816, Wistar offered Horner the position of dissector at $500. Horner's fortunes were henceforth identified with the department of anatomy in the University of Philadelphia. On Wistar's death in 1818, John Syng Dorsey became professor of anatomy, and Horner rose to the position of demonstrator. Dorsey died a few months later, and his uncle, the distinguished Philip Syng Physick, left the position of professor of surgery to assume the chair of anatomy. Horner was promoted again, to the position of adjunct professor (1820); shortly afterward he became dean of medical school, and eleven years later he succeeded Physick as professor of anatomy, himself.

During this time, Horner also acquired a private practice in the city. It is interesting to note that in his early days, before he had quite settled down to an academic life, he had wished to accept a position as ship surgeon in an East Indiaman. The longing to travel proved almost too strong a temptation. He refused only because his feeling of moral obligation to his chief, Caspar Wistar, was stronger. A deeply pious person, constantly subjecting his own private thoughts to the sternest

critical examination, he entered this note in his journal in 1816: "My refusal was the result of my sense of obligation and honorable intentions with regard to Dr. Wistar. It is said that honesty is the best policy; here, then, is a trial of the rule." Years later, on Jan. 1, 1832, he subjoined to this entry the naively triumphant addition, "See note of Trustees of the University of Pennsylvania appointing me Professor of Anatomy, *vice* Dr. Physick, resigned." He had just succeeded to the first chair in anatomy, one of the outstanding positions in the teaching of medicine in the country.

In the intervening years he had married, acquired a good financial competence, traveled abroad, and done most of his best work. The

WILLIAM EDMONDS HORNER
1793-1853

distinguished surgeon and American medical historian Samuel Gross spoke of him several decades later as the most accomplished anatomist that this country had produced. Horner had reedited Wistar's "Anatomy" (1823), published a "United States Dissector or Lessons in Practical Anatomy," which was to go through four editions, and put forth a monumental "Treatise on the Special Anatomy of the Human Body" (1826), of which ultimately eight editions appeared. He had written a short article, which has preserved his name in anatomic nomenclature, on a muscle of the orbit now known as the "tensor tarsi" or "Horner's muscle." He had published numerous articles of import for pathology in the *American Journal of the Medical Sciences,* and written the text in this subject in 1829 which is the subject of this paper.

The origins of this book may be traced to several sources. The motive of publication was given by Horner himself in the Preface:

> The following work is intended more especially for the use and guidance of practitioners of medicine. . . . It treats of a department in our science comparatively strange to the mass of medical men, and for which there is no sufficient provision by the plan of instruction, in any of the numerous colleges of our country. Pathological anatomy, by the recent organization of the most improved schools of Europe, has taken a high and commanding attitude. The numerous observations which have been made in it, and the increased skill arising from various and accumulating experience, have at length enabled its cultivators to systematize its facts, and to make a close and instructive application of them to nearly every case of disease, which they are called upon to treat. It is now almost universally conceded to be the light and test of every opinion in medicine; and when the latter fails to harmonize with it, whatever may be the ingenuity of the opinion, it is not likely to obtain either permanent attention or consideration, and must perish in that oblivion which has buried so many medical theories. The modern pathologist has ceased to consider disease as an independent existence, which may insinuate itself into the human body; and whenever its name is mentioned, he invariably associates with it the existence of a change or lesion in the structure of some part of the body, which in fact, is the disease itself.

It was indeed lamentably true that pathology was a science comparatively strange to American physicians, and unprovided for in university medical instruction. This was, at least in part, the fault of the very school of medical thought responsible for the high position of the medical department of the University of Pennsylvania, i.e., the set of doctrines originating in Edinburgh. The speculative pathology of the Scotch physician John Brown, good enough for Benjamin Rush, was still dominant and only beginning to give place to the new learning on pathologic anatomy coming from Paris. Philadelphia physicians, groping in their own experience for this new light, turned to the anatomists for help. Horner made many postmortem examinations at their request in cases that had been found puzzling. He took the professional ethics of this relationship most seriously, as may be seen from the following earnest expression of his views on the obligations involved (from the preface of the "Treatise on Pathological Anatomy"):

> I know in fact no higher mark of the confidence which one physician reposes professionally in another, than an examination subsequent to treatment: the errors and misconceptions of the prescriber are there fully exposed when they have occurred, and his reputation stands more or less committed. Happily for our profession, breaches of confidence on this point are very uncommon; in my own personal observation, I have never known of one, and such a betrayer would be justly held in so great abhorrence, that his first treachery would also be his last.

Horner knew that the science of medicine would inevitably extend to its practice, and he saw pathologic anatomy destined to become the basis of scientific medicine. His European trip of 1821 must have opened

his eyes to this certainty. All his later writings indicate that French pathology, as developed by Bichat and his successors of the following generation, made a profound impression on him. His new views, however, marked a great departure from his original teaching at the hands of John Spence and the Edinburgh trained masters in Philadelphia.

TREATISE

ON

PATHOLOGICAL ANATOMY.

BY

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PHILADELPHIA:

CAREY, LEA & CAREY—CHESNUT STREET.

1829.

Fig. 2.—Title page of Horner's "Treatise on Pathological Anatomy."

The strong feelings of Spence cropped out in a letter which Horner cited in writing his old teacher's obituary. The recipient of this letter is not named, but was presumably Horner himself. The obituary reads:

> Our colleague (that is, Spence) was much attached to the theories and modes of practice in which he had been educated. Having imbibed his first principles in the school of Cullen and under his immediate teaching, they never were obliter-

ated from his mind, and were to him the infallible evidences and tests of medical soundness and truth. In a letter to a correspondent of a recent date, he says: "Your devotedness to French pathology may lead you into error; you may thereby run the risk of the young advocate of Brown's system, that of a charge of servility and the want of original eclectic power. I fear the consequences of the present rage for this ultra French pathology, which seems to rest almost everything on a hypothetical basis. In these remarks I confine myself to the doctrine of idiopathic fever—of gastro-enteritis.

"When John Brown published his Elementae Medicinae, referring all diseases to tonic and atonic, he observed that the bilious remittent fever of hot climates was a disease of debility and must be treated at once by stimulants. In the second edition of his Elementae, he says in a note that he must correct his former prescription, for that some of his young American friends and pupils (and the American students were devoted to him) informed him that without previous evacuations from the stomach and bowels, his stimuli would destroy such patients—and he followed their advice. Can you suppose that old practitioners like myself would surrender a long-tried and successful practice in bilious fevers for this novel system of Broussais—no—never. But I cannot bring myself to believe that you embrace the ultra French pathology to the exclusion of prescriptions sanctioned by men of intelligence, observation, and nice discrimination. If you did I would say

"Incedis per ignes
Suppositos cineri doloso."

"I agree with you that such lectures (meaning lectures on pathology) should be incorporated into your plan of public education, and rendered essential to obtaining a diploma.

"The success of your University has caused much dissatisfaction and envy—and now they wish to injure its fame, by giving out that the ultra pathology of France, is the ruling passion of your professors."

The mortality statistics collected in 1829 for the preceding year in Philadelphia throw sufficient light on the lack of anatomic localization of disease in America at this time. The ten chief listed causes of death were (out of 7,033 deaths): consumption, 581; stillbirth, 321; convulsions, 315; cholera, 291; debility, 286; inflammation of the lungs, 130; dropsy in the head, 110; fever, 118; smallpox, 107 and bilious fever, 105.

Also listed in this imperishable record were: atrophy, 38; decay, 16; old age, 64; cancer, 18; casualties, 19; sudden, 55; found dead, 29; mania a potu, 82; drinking cold water, 5; hives, 71; teething, 7 and unknown, 71.

Attention in passing should be called to the item cholera. This was fearfully prevalent at the time, and Horner himself in succeeding years did much toward its control, his investigations including an abundant experience in the postmortem examination of this disease. After the epidemic of 1832, the City of Philadelphia presented him with a magnificent inscribed silver pitcher in recognition of his services.

Horner's "Treatise on Pathological Anatomy" was by intention and in effect an entering wedge for improvement in the situation revealed

ANALYTICAL INDEX.

Fig. 3.—Table of Contents of Horner's "Treatise on Pathological Anatomy."

by these figures. As a teacher of young men who were to become physicians, and as a prosector for fellow physicians, he felt the need of an American textbook in the subject. He had already published a number of articles which he felt might well be incorporated in such a book. He had for several years been particularly interested in modifications in the appearance and texture of the gastro-intestinal tract. One can see here the influence of Broussais, who had made a profound impression on Horner in Paris in 1821. The latter, to his credit, however, never pushed Broussais' doctrines of gastro-enteritis to the absurd extremes of the famous French clinician. The *American Journal of the Medical Sciences* opened in 1827 (it had been previously published under another name) with an article by Horner, who was one of the thirty-nine collaborating editors of the new journal, entitled, "Inquiries into the Healthy and Diseased Appearance of the Mucous Membrane of the Stomach and Intestines." Colored plates were appended. This article and a later one entitled, "An Inquiry into the Anatomical Character of Infantile Follicular Inflammation of the Gastro-Intestinal Mucous Membrane, and Its Probable Identity with Cholera Infantum" (1829), were copied, with a few additions, but otherwise practically verbatim, into the "Treatise on Pathological Anatomy" as chapters 10 and 11.

A detailed analysis of the chapters of this book would be unnecessarily tedious. For the purposes of this review, it may be divided into three parts, although it is not so divided in the organization of the work. The first of these might be entitled General Pathology; the second deals with Horner's own contributions and views in specific fields, and the third is devoted to a summary of the pathologic doctrines of other investigators in respect to some of the most important portions of the subject. These are almost without exception French. The views quoted are taken directly from the famous writings of Bichat, Corvisart, Laennec, Louis, Andral and others, with abundant quotations from French works like those of Gendrin and Roche and Sanson, which have long since been forgotten. Horner's information on the heart is Corvisart's, his picture of diseases of the chest is Laennec's, his knowledge of diseases of the central nervous system comes from Lallemand, and so forth. It is true that in most instances he could not have done better, and the greatest strength of the book rests in the weight derived from these foreign authorities. His summary of their views is abundantly supplemented from his own post-mortem experience, chiefly from his service in the infirmary of the Philadelphia Almshouse. Eighty-nine partial or complete records of necropsies from Horner's experience appear in the book.

It must be confessed at once that as an independent pathologic anatomist Horner was deficient. He was an excellent normal anato-

mist, extremely well versed in the exactitudes of that science, but in the deductions and subjective evaluation of tissue changes, which are basic to pathology, he fell short. His protocols of necropsies are, for the most part, purely descriptive, and do not achieve their object of clinical explanation. His picture of inflammation of the gastro-intestinal tract is largely erroneous. Indeed, one may perhaps hold Horner partly responsible for the familiar fallacy of naming acute gastritis as a cause of sudden death, still all too common in coroner's records. Although he recognized "active and passive congestion" of capillary beds, and was familiar with John Hunter's work on postmortem digestion of the stomach, he designated as inflammation what appear to have been simple postmortem settlings of blood in the wall of the bowel, and wrote voluminously on mollescence of the stomach. He attached a great deal of significance to the common punctate extravasations of blood in the gastric mucosa, and took for manifestations of primary disease what we now recognize as simply the necessary anatomic results of the vastly overenergetic purgings and bleedings and starvings of the current medical practice. It is interesting to note that in a brief history of pathologic anatomy with which Horner prefaced his treatise on the subject, he criticized in an able manner such writers as Bartholin, Bonet and Morgagni for the errors into which he later fell himself. Nevertheless, his necropsy experience covered an enormous range in pathologic anatomy, and must have made Horner and the physicians whom he assisted familiar with the gross appearance of carcinomas of the esophagus, stomach and rectum, tuberculosis of the lungs, larynx and pericardium, pleural and peritoneal effusions, aneurysm of the aorta, calcification of the aortic valve, pericarditis and many more common lesions, and his book unquestionably went far to spread this knowledge in a profession whose members had very rarely gone further in postmortem experience than routine dissection for instruction in normal anatomy.

The first nine chapters of the book deal with the principles and organization of pathology. Although the classifications of lesions proposed is a borrowed one, critical examination of this reveals a good deal of self determination in the analysis of types of lesion. The classification is the clumsy one favored in continental Europe in this period, stressing abnormalities from a mechanical point of view. Horner at the outset proposed to limit his discussion to the first of thirteen types of lesion, viz., irritation. This, in turn, is divided into six subtypes: inflammation (or phlegmasia), hemorrhage, subinflammation, neurosis, nutritive irritation and secretory irritation.

Attention may profitably be confined to Horner's views on the first of these. Inflammation is the keystone of pathology, and it is probably

sound to evaluate any set of doctrines in the science by the character of the consideration devoted to this phenomenon.

Horner himself counted acute inflammation as the beginning of 90 per cent of disease. He cited its four classical manifestations, but rightly directed attention to the fact that these are seen typically only in inflammations of the cellular, i.e., subcutaneous connective tissue, and are not necessarily characteristic of inflammation elsewhere. He said: "Pathologists have been led into the error of adopting the type of inflammation in it (cellular tissue) as the type of inflammation in other parts. They have stumbled and fallen at the threshold of their inquiries by expecting identical phenomena in all other tissues, even in those least resembling it in composition and mechanical arrangement."

In a brief and accurate fashion, well suited to didactic teaching, Horner listed the several ways in which inflammation may subside. Few references are cited. His generalizations appear to come from both reading and observation. His treatment of the subject is almost entirely descriptive, however, and in striking contrast to the lengthy teleologic approach of another work which at once comes to mind, that of John Hunter, who saw design in every one of the phenomena of inflammation.

Horner was certainly familiar with Hunter's masterpiece with the blood-curdling title "Blood, Inflammation and Gun Shot Wounds," which was widely read in this period. It might be supposed that the truly spiritual view of the phenomena of inflammation taken by Hunter would have appealed strongly to Horner, by nature a devout conformer to religious convention. But Horner must have considered this aspect of Hunter's treatment of the subject impractical in a textbook for practitioners. He had nothing to say of the beneficent principles underlying the manifestations of inflammation, which seems to have appeared to him a wholly malignant process, indeed as the cause of disease itself, and not as a reaction to a still prior inciting agent. Horner's insistence on a simple descriptive treatment of inflammation, and his failure to take a physiologic view of the subject, make his initial chapters dull reading. He could not foresee, of course, the cellular pathology and bacteriology of today, and the present frankly vitalistic immunology with its antibodies, phagocytes, etc. But a rich physiologic background for views on inflammation was available to him, of which he took no advantage. In this respect, the highly accurate descriptive French pathology, which had seemed to him such a torch in the current lack of illumination on the nature of disease, held him back.

It would be interesting to know a little more of the reception of Horner's book in his own time. It was reviewed by John Godman in the *American Journal of the Medical Sciences;* but the review is devoted largely to Horner's eminent qualifications for writing such a book and scarcely at all to the merits of the book itself. Ten years

after the publication of Horner's work, a far better treatise on the subject appeared in Samuel Gross's "Elements of Pathological Anatomy," which became immediately the standard American text.

To form a just view of Horner's book, one should compare it with those appearing elsewhere at approximately the same time. It suffers in the comparison. It was published in the same year as the two volumes on typhoid fever by Louis of Paris. The latter was by far the abler product. Richard Bright's "Report of Medical Cases," with its classic account of nephritis, had been out a little less than two years. Horner gave no indication of having seen or profited by this far more inspiring compilation. Cruveilhier's "Pathological Anatomy of the Human Body" was in preparation, and on publication proved to be the product of a much superior hand.

Nevertheless, with all its defects, the "Treatise on Pathological Anatomy" was a courageous piece of pioneering, wholly in accord with America's frontier traditions. Horner, one of the humblest of his profession in the estimation of his own capacity, seeing a fundamental weakness in American medicine, and nobody to improve the situation but himself, quietly assumed the responsibility. For ten years his product stopped the gap, and in that time must have been a constant stimulus toward a pathologic-anatomic point of view in American practitioners of medicine, if not toward an exact interpretation of all the symptoms of illnesses encountered, or an understanding of all the lesions seen.

Horner lived twenty-four years after the publication of his "Treatise on Pathological Anatomy," devoting the major share of his literary energy henceforth to the elucidation of normal structure. During these years his health became steadily worse, and his temperament more melancholy. Migraine headaches and fits of indigestion, which had distressed him since childhood, increased in severity. How his physical condition affected his working capacity only Horner himself knew, as he gave little outward sign of his trouble. But he did once complain that "a man who suffers from pain in the head during three-fourths of his waking existence cannot be expected to perform much work without great discomfort and dissatisfaction." He grew more introspective and self-deprecating. He spent hours in prayer, in the morbid feeling that he must be undergoing punishment for his sins. To the best of his remembrance, he had always walked faithfully in the sight of men, but had he done so, he repeatedly asked his inmost self, in the sight of God? In 1839, he joined the Roman Catholic Church. It was no sudden resolve, but the result of years of pondering, and partly the aftermath of his experiences in the cholera epidemics of Philadelphia, where time after time he had seen Catholic priests and sisters, with the characteristic self-effacement of their creed, alone standing at their posts in the universal panic inspired by this fulminating disease.

He continued his teaching to the end of his life. Never a fluent teacher, he was always an accurate one. His own anatomic preparations were faultless, and he tolerated no carelessness in his assistants. His lectures must have been monotonous, but through insistent repetition he drove his lesions home. A gradual failure of the heart, with increasing dyspnea, added to his disability in his declining years. In the last year of his life, he used to appear before his classes with edematous legs bandaged almost to the hips. The death of a beloved daughter in 1852 broke the morale of this faithful laborer, beyond recovery. Even from his bed, however, he continued to attend to the needs of his students, and three days before death assisted in an examination. An acute abdominal attack hastened his end, a terminal peritonitis carrying him off on March 13, 1853, a broken, arteriosclerotic old man, whose heart had long been decompensated and who had aged years before his time.[1]

His services to anatomy have gradually been forgotten, except as commemorated in the relatively insignificant "Horner's muscle." The great contributions to medical education by this man, who was for over thirty years dean of the first and in its time foremost medical school, are scarcely recalled. Still less is it now remembered that it was he who truly introduced modern pathology to his profession in America, by example if not by innate capacity. In his impressionable twenties he had been remolded in the training of the great French school of pathology, and, practically alone in his own country, he set out to impregnate American medicine with the new learning, the epitomized expression of which by a leader of that school (Jean Cruveilhier) is set down in the preface of his treatise: A physician without pathologic anatomy could, indeed, be ever so skilful in practice, but although he might see many patients, he would see no diseases.

1. The following account of his final illness was given by Dr. Samuel Jackson on Oct. 10, 1853, in an address to the faculty and students of the University of Pennsylvania ("'A Discourse Commemorative of the Late William E. Horner, M.D.' Published by the Class"):

"It is somewhat remarkable that the death of Doctor Horner was not the immediate result of the chronic affection under which his constitution had broken down. He had complained about the 10th of March of pain in the abdomen on the left side. On the night of the 12th it suddenly assumed an intensity that led to the suspicion of peritonitis from a perforation. He sank exhausted by unceasing and unmitigable suffering the evening of the next day, March 12, surrounded by his sorrowing family and relatives.

"Examination after death revealed the existence of entero-peritonitis, with mortification of the small intestines. This new condition was the direct cause of death, and had suddenly supervened on the original disease."

Speculation on the cause of this peritonitis is enticing, but in the lack of a more thorough clinical and postmortem record would be equally uncertain.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths.—On his eightieth birthday, April 8, William H. Welch, professor of the history of medicine, Johns Hopkins University, was honored by simultaneous celebrations in London, Paris, Berlin, Leipzig, Tokyo, Peiping, Baltimore, Cincinnati, New Haven, New York and Washington, D. C. At the Washington ceremonies, addresses were made by President Hoover and Simon Flexner, with a response by Dr. Welch.

Andrea Saccone has been appointed assistant professor of pathology in the New York Homeopathic Medical College.

A memorial meeting in honor of Richard Mills Pearce, Jr., was held April 15, 1930, at the Rockefeller Institute for Medical Research, New York, at which addresses were made by George E. Vincent, David L. Edsall, Howard T. Karsner and Simon Flexner.

The Academy of Medicine of Cleveland has conferred honorary membership on George Neil Stewart, director of the Cushing Laboratory of Experimental Medicine at Western Reserve University.

On retiring from the U. S. Army, May 1, Lt. Col. Fielding H. Garrison, medical historian and assistant librarian in the Army Medical Library, Washington, D. C., from 1889 to 1922, will assume the duties of librarian of the Welch Medical Library, Johns Hopkins University.

Herbert M. Evans, professor of anatomy in the University of California, has received an honorary doctorate from the medical faculty of the University of Freiburg, in recognition "of his conspicuous anatomic and biologic discoveries, especially in the sphere of vitamin research."

Karl Landsteiner, a member of the Rockefeller Institute for Medical Research, New York, was awarded on March 14, the anniversary of Ehrlich's birth, the Paul Ehrlich gold medal of the Paul Ehrlich Foundation of Frankfort-on-the Main, in recognition of his work on human blood groups and his haptin theory of immunity.

The resignation is announced of Roger Griswold Perkins, professor of bacteriology and preventive medicine and head of the department of bacteriology and hygiene of the School of Medicine of Western Reserve University. Dr. Perkins desires to be liberated from university duties so that he may have more time for special studies. He will live at Wakefield, R. I.

Congress of the International Society for Microbiology.—The date of the first congress, which is to convene in Paris, has been changed again, this time to July 20 to 25, 1930.

American Society for Experimental Pathology.—At its recent meeting in Chicago, the following officers were elected for the ensuing year: president, Frederick L. Gates; vice-president, Samuel R. Haythorn; secretary-treasurer, C. Philip Miller, Jr., and councilors, Peyton Rous and Carl V. Weller.

Prize for the Study of Goiter.—Beginning this year the American Association for the Study of Goiter will award a cash prize of $300 annually for the best original thesis dealing with some phase of the goiter problem. Theses should be submitted by June 1 to Dr. Walter M. Simpson, Chairman of the Essay Committee, Miami Valley Hospital, Dayton, Ohio. The award will be given immediately following the coming meeting of the association which is to be held in Seattle, July 10 to 12, 1930.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE EXPERIMENTAL PRODUCTION OF ABSCESS OF THE LUNG. ELLIOTT C. CUTLER, Am. J. Dis. Child. **38**:683, 1929.

The surest way to produce an experimental pulmonary abscess is by the use of an infected embolus. No abscess is formed following aspiration and insufflation of infected material into the air passages unless there is complete bronchial obstruction with subsequent atelectasis and anaerobiasis. It is suggested that an embolus from a septic field causes the original lesion and that this becomes a chronic abscess only by being secondarily infected by aspiration of organisms from the mouth and upper respiratory tract.

J. N. PATTERSON.

DIETARY CONTROL OF DENTAL CARIES. J. D. BOYD, C. L. DRAIN and M. V. NELSON, Am. J. Dis. Child. **38**:721, 1929.

Dental caries has been arrested in many instances, under divergent conditions of health and environment, by the ingestion of diets high in mineral and vitamin content. All diets were designed to give adequate proteins and calories, but in other respects they varied widely. The arrest usually becomes apparent after about two months of dietary control. On the basis of the clinical and experimental observations, it is thought that active caries should be viewed as indicative of nutritional deficiencies. These deficiencies may not make themselves obviously apparent in any other way. Yet when the food intake is made adequate, caries will become arrested, and in other respects there will be evidences of better health.

AUTHORS' SUMMARY.

DIFFERENCES BETWEEN HIGH AND LOW INTESTINAL OBSTRUCTION IN THE DOG. J. J. MORTON, Arch. Surg. **18**:1119, 1929.

In his preamble concerning the mechanism and etiology of the toxemia of intestinal obstruction, the author concludes that the rôle of bacteria has not been excluded. His investigation is concerned with anatomic and physiologic differences between the duodenum and the ileum, the object being to show that there is an anatomic explanation for the more rapidly developing toxemia in high obstruction as compared with low obstruction. The vascular supply and capillary bed were injected in equally measured segments of the lower duodenum and terminal ileum. This showed that the arterial supply and the capillary network were much greater in the duodenum than in the ileum. By a similar method of injection, he was able to demonstrate that the duodenal villi were thicker and much more closely placed than in the ileum. The ability of the duodenum to withstand intraduodenal pressure seemed to be somewhat greater than that of the ileum. The musculature in the duodenum was about one-third again as great as that of the ileum and the wall was thicker. The secretory powers of the two portions were compared in obstructed loops, and it was found that the duodenum secreted anywhere from five to ten times as much fluid as the comparative loop of the ileum. This in itself would produce a great pressure in the duodenum and outweighs the resistance of the duodenum to pressure; hence necrosis and perforation always occurred in the duodenal loop before they did in the loop of ileum. The mechanism which caused the more rapidly developing toxemia may be explained by the intraduodenal pressure squeezing the toxins through the wall into the circulation. The latent period in which there are no symptoms is taken up by the secretion of fluid and bacterial growth. Then the absorption of histamine and histamine-like bodies and the

products of bacterial growth occurs, and with it the engorgement and edema and peculiar dusky cyanosis of the wall develops. Nevertheless, no conclusions could be drawn from his investigations on the exact pathway by which the toxins are absorbed.

N. ENZER.

EXPERIMENTAL DIABETES INSIPIDUS. E. B. TOWNE, Arch. Surg. **18**:1165, 1929.

An attempt was made to produce diabetes insipidus in dogs by dividing the stock of the pituitary high enough up so that all epithelial cells of the pituitary gland would be detached from the base of the brain. Ten dogs were operated on, and six survived. Polyuria lasted from four to twenty-one weeks. At postmortem examination, serial section of the hypophysis and base of the brain showed that the division of the stock had been high enough to detach all cells of the pars tuberalis in only one of the dogs. In the others small groups of cells had been left attached to the under aspect of the third ventricle. Nevertheless, a permanent polyuria did not develop. The finding of eosinophilic cells in the nest of epithelial cells found at the base of the brain was interesting. Also, a few similar cells were found in the pars intermedia and pars tuberalis which had become reattached to the uninjured base of the brain in one dog. The author discusses the various theories concerning the rôle of the pituitary and the base of the brain in diabetes insipidus, and from his experimental work could not draw any definite conclusions. The important thing is that the pars tuberalis cannot be dismissed as having no influence, and it does seem that from his experiments the neurogenic origin of this syndrome can be disproved, since the polyuria ceased when the pars intermedia became reattached.

N. ENZER.

SEPARATION OF GROWTH-PROMOTING HORMONE FROM THAT INDUCING PREMATURE ESTRUS IN THE ANTERIOR PITUITARY GLAND. T. J. PUTNAM, Arch. Surg. **18**:1699, 1929.

This work is chiefly concerned with the repetition of the experiments of Evans and Long (*Anat. Rec.* **21**:62, 1921). It was found that by using an alkaline extract of the anterior pituitary on dogs a condition of acromegaly was produced. These dogs increased in weight and developed enlargement of the acro parts, polyphagia, asthenia, sialorrhea and spontaneous lactation. Estrus did not develop. Autopsy showed skeletal overgrowth, splanchnomegaly, hyperplasia of the thyroid, adenomas of the suprarenal glands, enlargement of the uterus and vagina and cysts in the ovaries, but no lutein tissue. The transplantation of fresh and old anterior lobe material in rats resulted in premature estrus, but did not produce it in animals that had been spayed. Putnam failed to demonstrate glycosuria in hypophysectomized rats in anterior hypophysectomy. In discussing the possibility of more than one hormone being present in the anterior pituitary, there seems to be evidence that an alkaline aqueous extract brings about different results from those following the implantation of the insoluble residue. The latter produces premature estrus, whereas the former causes growth of the mesodermal tissues.

N. ENZER.

STUDIES IN ACROMEGALY. T. J. PUTNAM, E. B. BENEDICT and H. M. TEEL, Arch. Surg. **18**:1708, 1929.

This article is concerned largely with a detailed autopsy description of a dog that received a daily injection of an aqueous extract of the anterior lobe of beef hypophysis for fourteen months. It grew to twice the weight of its control. At autopsy, it presented all the physiologic and skeletal changes of acromegaly. The hyperplastic change in the thyroid was more striking than that seen in human material, and also the unusual enlargement of the uterus and vagina. It is possible that the extract used here contained an estrus-producing hormone isolated by Evans and Simpson.

N. ENZER.

CEREBROSPINAL FLUID CHANGES IN COMPOSITION AND DRAINAGE AFTER INTRAVENOUS ADMINISTRATION OF VARIOUS SOLUTIONS. R. G. SPURLING, Arch. Surg. **18**:1763, 1929.

A freely draining cisterna magna was produced in dogs and then intravenous injections of 50 per cent dextrose, 15 per cent and 0.45 per cent sodium chloride, Ringer's solution and distilled water were given. Isotonic solutions increased the drainage and diluted the cerebrospinal fluid. Hypertonic solutions at first increased the drainage, but this was reversed and the spinal fluid became concentrated. In one of these experiments air was drawn up into the ventricles. Hypotonic solutions produced the same effect as Ringer's solution, but distilled water produced very little change.

N. ENZER.

COMPARISON OF THE PATHOLOGICAL EFFECTS OF PROLONGED EXPOSURE TO CARBON MONOXIDE WITH THOSE PRODUCED BY VERY LOW OXYGEN PRESSURE. J. ARGYLL CAMPBELL, Brit. J. Exper. Path. **10**:304, 1929.

It is shown that in chronic carbon monoxide poisoning in animals the pathologic effects resemble very closely those of prolonged exposure to very low oxygen pressure in the inspired air; the main changes are venous congestion with atrophy of certain cells (e. g., liver, heart muscle near the epicardium), edema and dropsy indicating that heart failure is the cause of inability to tolerate prolonged exposure to carbon monoxide. The organs showing most marked congestion and its sequelae are the liver, lungs, heart muscle near the epicardium and the brain. Haldane's view that carbon monoxide acts purely by interfering with the oxygen supply to the tissues is supported.

Power to tolerate carbon monoxide — just as in the case of low oxygen pressure in the air — depends on the ability of the vital organs, particularly the heart, to continue to function under a low tissue oxygen tension; tissue oxygen tension is not brought back to normal level by so-called acclimatization under severe degrees of oxygen want.

AUTHOR'S SUMMARY.

PULMONARY TUBERCULOSIS AND ACID INTOXICATION, PARTICULARLY LACTIC ACID. F. POMPLUN, Beitr. z. Klin. d. Tuberk. **72**:324, 1929.

In patients with slight lesions, the lactic acid values in the venous blood are nearly the same at rest and during exercise. But in far advanced cases, the difference between rest and exercise becomes large; in such cases the values are elevated above the normal, even at rest, the elevation being parallel with the amount of pulmonary involvement. In the anaerobic phase of muscular labor glycogen is decomposed to lactacidogen and then to lactic acid. For the oxidation of the latter or for its resynthesis to glycogen, oxygen is needed. Previous studies on gases of the blood have demonstrated the fact that with increased pulmonary involvement, a relative or absolute deficiency of oxygen exists in the arterial blood. This oxygen deficit is the cause for the accumulation of lactic acid, since oxygen is necessary for its normal disposal. This mechanism of decompensation is evident at first only during exercise, and accounts for undue muscular fatigue; with progressing lesions, decompensation exists even during rest in bed; in such cases, the patients are dyspneic at rest.

MAX PINNER.

PATHOLOGIC EFFECTS OF IRRADIATED ERGOSTEROL. HELENE HERZENBERG, Beitr. z. path. Anat. u. z. allg. Path. **82**:27, 1929.

The discovery of the antirachitic action of irradiated ergosterol was followed by observations that indicated that this substance has a toxic effect when administered to mature rats in relatively large doses. Among the tissue changes noted was calcification of the aorta. It was primarily to study the vascular changes and to compare them with those of arteriosclerosis and those caused experi-

mentally by cholesterol feeding that the experiments reported by Herzenberg were undertaken. Young and mature rats were used. The ergosterol was introduced directly into the stomach by means of a catheter in variable doses of from 5 to 100 mg. Some of the animals were kept on the usual mixed diet, some on a diet low in calcium and some on the mixed diet to which an excess of calcium carbonate was added. Kreitmaier and Moll had noted pathologic effects in 100 per cent of the animals to which they had administered irradiated ergosterol. Of fifty-five animals used by Herzenberg in her series of experiments, all but two showed alterations of varying degrees of severity. The manifestations of a general effect consisted in loss of appetite and weight, roughening of the coat of hair, diarrhea and hemorrhagic crusts about the nose and eyelids. Young and adult rats on a high calcium diet withstood the effects better and lived longer than adult rats on a mixed diet; some of the former lived from fifty to sixty-four days. In adult animals on a mixed diet, large daily doses of ergosterol had an acutely toxic effect, death occurring as early as the sixteenth day. In such animals necrosis with leukocytic infiltration was noted in the striped muscle of the heart and diaphragm and in the smooth muscle of the aorta, rarely in the smooth muscle of the gastro-intestinal tract and never in that of the urinary bladder or uterus. In experiments of longer duration, calcium was deposited in the media of the aorta and its branches down to the smallest arteries except those of the skin, in the veins, in the heart muscle and in the renal, bronchial and gastric epithelium, in the latter situations evidently as the result of calcium excretion. Calcium deposition occurred in the media of the vascular system, even in the absence of necrosis of muscle fibers. The elastic fibrils of the media also became impregnated with calcium. Proliferative changes were not noted in the intima. The arterial process was a pure medial calcification, which the author does not consider arteriosclerotic in character. The widespread calcification might be the result of increased calcium assimilation under the influence of ergosterol or of increased mobilization of calcium from the bones. The latter is the explanation accepted by the author, the mobilization being probably the result of an acidosis caused by the ergosterol. Similar arterial changes could not be brought about by the use of epinephrine or chloramine.

O. T. SCHULTZ.

IRRADIATED ERGOSTEROL EXPERIMENTS. M. SCHMIDTMANN, Verhandl. d. deutsch. path. Gesellsch. **24**:75, 1929.

Experimental results seem to indicate a discrepancy between the results of irradiated ergosterol feeding in human beings and experimental animals. There were marked fatty changes in the arteries of rabbits and cats after from eight to fourteen days of feeding two drops of irradiated ergosterol per day. In young animals, death occurred in two ways after large doses. Some animals died a sudden toxic death after several days, and postmortem examination showed parenchymatous degeneration and petechia in their organs. Others had chalk cylinders in their kidneys and calcification in the parenchyma. At times this was accompanied by bladder stones and pyonephrosis.

GEORGE RUKSTINAT.

POSTOPERATIVE KETONURIA. M. MOGILEW, Zentralbl. f. Gynäk. **52**:1216, 1928.

In 100 surgical gynecological cases a preoperative ketonuria was observed in 11 per cent of the cases and a postoperative one in 67 per cent. Starvation, increased by the use of laxatives, and the psychic status of the patient are regarded as the cause of the preoperative ketonuria, while starvation, operative trauma, anesthesia, psychic status and other factors influencing the vegetative nervous system are considered as cause of the postoperative ketonuria. The ketonuria lasts usually to the fourth day after operation. Preoperative prophylactic treatment with insulin and dextrose resulted in disappearance of the postoperative ketonuria.

W. C. HUEPER.

Pathologic Anatomy

ACUTE OBSTRUCTION OF THE CORONARY ARTERY. JAMES B. HERRICK, Am. Heart J. **4**:633, 1929.

This condition is usually caused by a thrombus in a vessel, the wall of which shows chronic retrograde processes. These chronic changes may not be the only factors in causing the thrombus to form. Other factors may be (1) emboli from intracardiac thrombi formed over myocardial infarcts, (2) infectious processes in other parts of the body, (3) coronary phlebitis and (4) physical and chemical changes in the blood. The outcome of the lesion depends not only on the suddenness and completeness of the occlusion but also on the size and location of the vessel involved, the amount of collateral circulation, the condition of the intact portion of heart muscle, and the capacity of the infarcted area to heal by scarring.

PEARL ZEEK.

DISTORTION OF THE BRONCHI BY LEFT AURICULAR ENLARGEMENT. J. M. STEELE and R. PATERSON, Am. Heart J. **4**:692, 1929.

Enlargement of the left auricle may exert pressure on the esophagus and main bronchi, but this phenomenon rarely gives rise to changes in the lung. However, it may frequently be found by x-rays and thus aids in the diagnosis of left auricular enlargement.

PEARL ZEEK.

INTESTINAL PNEUMATOSIS. ROBERT A. MOORE, Am. J. Dis. Child. **38**:818, 1929.

Four cases of intestinal pneumatosis in infants are reported. The pathologic picture is the presence of gas in endothelial lined cysts of the intestinal wall with a chronic productive inflammation in the surrounding tissue. The gas is derived from the intestinal lumen and enters the wall by a mechanical process through an ulceration in the mucosa.

AUTHOR'S SUMMARY.

THE HEPATIC LESION IN ECLAMPSIA. W. J. DIECKMANN, Am. J. Obst. & Gynec. **17**:454, 1929.

It is assumed that incompletely digested proteins, placental or intestinal in origin, find their way into the circulation and cause damage to the hepatic endothelial cells and shorten the coagulation time of the blood. These substances are of greatest concentration in the portal circulation and cause thrombosis in the larger and smaller portal branches of the liver and peripheral necrosis of the hepatic lobule. Histologic changes in the liver of dogs that closely resemble those of eclampsia may be caused by injecting tissue fibrinogen directly into the portal vein.

A. J. KOBAK.

DECIDUAL FORMATION ON THE PERITONEAL SURFACE OF THE GRAVID UTERUS. J. HOFBAUER, Am. J. Obst. & Gynec. **17**:603, 1929.

Ectopic decidual cell formation was noted in fifteen of twenty uteruses. These cells were located in an area roughly triangular on the posterior surface of the uterus in the folds made by the broad ligaments and uterus with the apex extending almost to the insertion of the ovarian ligament. Grossly, this area looks rough and has a dull sheen. The decidual-like cell has its origin in the cells which are present in the connective tissue layer beneath the peritoneal mesothelium. The cells are spindle-shaped with a dark ovoid nucleus and scanty cytoplasm. They may also simultaneously undergo metaplasia into unstriated muscle fibers. This cell is therefore considered to be an undifferentiated type of cell retaining its mesenchymal potentialities and responds to varying stimuli to form either decidual cells or muscle fibers. The cells of the peritoneal endothelium in some cases

were observed to undergo metaplasia and become cylindric and closely resemble that of the decidua vera. The author discusses the part played by hormones in producing these changes particularly that derived from the anterior lobe of the hypophysis.

A. J. KOBAK.

OBLITERATION OF THE VERMIFORM APPENDIX. C. A. HELLWIG, Am. J. Obst. & Gynec. **18**:332, 1929.

Of 859 appendixes obtained at operation, 60, or 7 per cent, showed atresia of the lumen. In 56 per cent only the distal third was occluded, and in the others the whole organ. The microscopic picture of the obliterated appendixes did not correspond to the descriptions as given by Ribbert, Sudsucki and Oppenheim, who studied autopsy material. Far from being uniform, it was of the greatest variety. In more than one half of the cases leukocytic infiltration and cellular granulation tissue was found which indicated that an inflammatory process had not completely subsided or that a healing stage of acute appendicitis was complicated by recurrence. Signs of healed appendicitis were found in about two thirds of the specimens and consisted of scar formation in the external layers. The histologic examination of the nonoccluded portion revealed pathologic changes in two thirds of the partially obliterated appendixes, and in one half of these the inflammatory changes were recent. All stages from acute purulent inflammation to the healing stage and to terminal fibrosis were present, leading to the conclusion that the atresia is the final stage of ulcerative appendicitis in which the epithelial tissue is completely destroyed.

AUTHOR'S SUMMARY.

ABNORMALITY OF THE CEREBRUM AND LEPTOMENINGES SIMULATING AN INTRACRANIAL TUMOR. R. C. BUCKLEY and E. M. DEERY, Am. J. Path. **5**:459, 1929.

A localized abnormality of the right cerebral hemisphere was found after death in the brain of an infant suspected during life of having a tumor of the brain. The lesion, when disclosed, was thought to be an unusual tumor, until the brain came to be sectioned. Had this lesion been exposed at operation, it might easily have been mistaken for an enucleable tumor, and had a fragment of one of the localized thickenings of the meninges been taken for immediate diagnosis, the tissue might well enough have been reported as a glioma.

AUTHOR'S CONCLUSION.

PATHOLOGIC HISTOLOGY OF ADRENALECTOMIZED CATS. H. E. MACMAHON and R. L. ZWEMER, Am. J. Path. **5**:491, 1929.

The gross and microscopic lesions following experimental adrenal insufficiency in cats (average survival ten days) are described. Briefly, they consist in fatty degeneration of the tubules of the kidney, lymphoid hyperplasia, moderate colloid distention of the thyroid and hyperplasia of the interstitial cells of the testis. The significance of these and other observations on experimental adrenal insufficiency is discussed in relation to "lipoid nephrosis," lymphoid hyperplasia and additional clinical syndromes.

AUTHORS' SUMMARY.

CONGENITAL ANOMALIES OF THE LIVER. H. E. MACMAHON, Am. J. Path. **5**:499, 1929.

Congenital anomalies of the liver are relatively infrequent. They may involve the biliary system, the liver cells or the stroma. Several of the more common types are described and explained on an embryologic basis. One type that is characterized by an increase and dilatation of the perioportal bile ducts, accompanied by an increase in connective tissue in the portal areas, may persist throughout life. Associated with this type of anomaly are the congenital cysts of the liver occa-

sionally seen at birth and also in later life. Moreover, this anomaly, with or without cyst formation, commonly accompanies bilateral congenital cysts of the kidneys.

AUTHOR'S SUMMARY.

CARCINOID TUMORS OF THE APPENDIX. C. L. WILMOTH, Ann. Surg. **90**:261, 1929.

In view of the present knowledge of carcinoid tumors, they are to be regarded in a similar relation to carcinoma as giant cell tumors are to osteogenic sarcoma. Emphasis is placed on the benign character of these growths. The origin of the carcinoid cells is explained on the conclusions which have been reached by Masson and Forbus by use of the ammoniacal silver stains. Although the tumors are practically benign, nevertheless they may assume malignant characteristics, but the author makes no statement regarding the cases which have been reported.

RICHARD A. LIFVENDAHL.

CONGENITAL MEDIASTINAL CYSTS OF GASTROGENIC AND BRONCHOGENIC ORIGIN. C. G. MIXTER and S. H. CLIFFORD, Ann. Surg. **90**:714, 1929.

Congenital mediastinal cysts occurred in three infants under 3 months of age. In two, a gastrogenic origin was warranted in that the cysts contained typical gastric mucosa. Their size was sufficient to cause displacement and atelectasis of the lung. The cystic fluid was opalescent, viscid, acid in reaction and had a specific gravity of 1.010; it was rich in polymorphonuclear leukocytes. This fluid differs from the oily material in dermoids, which in addition contain cholesterol crystals or squamous epithelium. The authors attribute these cysts to a pinching-off of outbuddings or diverticuli of the foregut with entoderm and mesoderm being carried downward by the growing lung thus lodging in the mediastinum or on the surface of the lung. The third case reported is a similarly located cyst but of bronchial origin which was covered by pseudostratified, ciliated columnar and low cuboidal epithelium overlying cartilaginous tissue. This type arises by a pinching-off of diverticuli of entoderm and mesoderm from the foregut in the region of or from the tracheal bud itself. The dermoid cysts are formed at an earlier period, and the teratoma represents a primative type of cell inclusion.

RICHARD A. LIFVENDAHL.

CHRONIC FIBROUS OSTEOMYELITIS. D. B. PHEMISTER, Ann. Surg. **90**:756, 1929.

Circumscribed areas of bone destruction that were filled with soft tissue, in eleven cases, afforded the opportunity for this study. In the earliest stages the cavity is filled with soft grayish-brown tissue containing fibroblasts, capillaries, polyblasts, old blood pigment and usually areas of more or less necrosis. The surrounding bone tissue may or may not respond by the formation of new bone. From two of the specimens, *Staphylococcus aureus* was cultured. Trauma could not be regarded as an etiologic factor. In the author's opinion, aseptic necrosis as the result of anemic infarcts is not sufficient to cause the lesion but possibly additional bacterial infection may be adequate to produce it. The organism is classed in the pyogenic group and therefore the typical inflammatory response is absent in the cytologic picture.

RICHARD A. LIFVENDAHL.

MASSIVE PULMONARY ATELECTASIS (COLLAPSE). HERMAN HENNELL, Arch. Int. Med. **44**:604, 1929.

The cases of massive collapse may be due to: (1) bronchial obstruction from within (foreign body, endobronchial neoplasm, blood clots, diphtheric membrane, etc.); (2) interference with respiratory movements from muscular paralysis or inhibition, faulty posture long continued, etc., leading to collapse from occlusion

of bronchial lumen by accumulated secretions; (3) extrabronchial pressure (neoplasm, aneurysm, enlarged lymph glands). In bronchial occlusion from whatever cause the alveolar air is absorbed and pulmonary collapse occurs.

AUTHOR'S SUMMARY.

THE PATHOLOGY OF THE PANCREAS IN NONDIABETIC PERSONS. SHIELDS WARREN, Arch. Int. Med. **44**:663, 1929.

The pancreatic lesions in 156 autopsies on unselected nondiabetic patients are summarized. Practically any lesion found in the pancreas of diabetic patients can be duplicated in the pancreas of nondiabetic patients, although the frequency of occurrence of lesions of the islands is much less in the latter group. Interstitial pancreatitis occurs too frequently in nondiabetic patients to be considered a characteristic lesion of diabetes. In many cases, lipomatosis is related to the amount of body fat. It is impossible from a study of the pancreas to diagnose the presence or absence of diabetes.

AUTHOR'S SUMMARY.

TUBERCULOSIS OF THE AORTA. LEYLAND J. ADAMS, Arch. Int. Med. **44**:711, 1929.

Thirty-six cases of tuberculosis of the aorta have been reported. The case cited here is the twentieth reported instance of tuberculosis reaching the aorta by extension from a tuberculous process outside the aorta. In this case the involvement extended to the media, but no rupture occurred. Clinically, syphilitic aortitis was suspected on account of the history, shortness of breath, pain, pallor and the positive Wassermann reaction.

AUTHOR'S SUMMARY.

DIENCEPHALIC AUTONOMIC EPILEPSY (CHOLESTEATOMA OF THIRD VENTRICLE). W. PENFIELD, Arch. Neurol. & Psychiat. **22**:358, 1929.

A woman, aged 41, had been suffering from occipital headaches since an accident to her head at the age of 5. When they were severe she would have attacks of dizziness. At the age of 28, during an attack the patient stiffened, fell under the table, was unconscious for several hours and apparently had a convulsion which involved the arms, legs and neck. At the age of 36 she began to show recurring seizures. The attacks would always begin by the patient asking for ice; then her face and arms would flush a deep red, respirations would become slow, tears would roll down the pillow, profuse general diaphoresis would appear and saliva would run out of the corner of the mouth. The eyes were open and protruding, the pupils were large and the pulse was strong and rapid. Gradually the flushing would fade, the pulse would become weak and slow. Respirations were of the Cheyne-Stokes type, and while the patient was breathing, goose-flesh would show on the forearms. The attacks were usually followed by shivering. Hiccup was an annoying and frequent symptom, especially after drinking. During some attacks the patient was unconscious and incontinent; the duration of the attacks was from five to twelve minutes. The repeated attacks resembled status epilepticus and could for a time be controlled by sodium bromide. Aside from the attacks the patient showed a papilledema, diminished hearing bilaterally, normal visual fields, enormously dilated lateral ventricles, absence of air in the third ventricle and disappearance of headaches after turning the head or changing its position. The diagnosis of tumor of the third ventricle was made, and the tumor was to be removed, but four hours before the time set for operation the patient died. Necropsy disclosed a tumor in the nature of a cholesteatoma in the anterosuperior portions of the third ventricle. It protruded into the foramen of Monro and pressed on the mesial anterior and superior aspect of the thalamus of each side. Histologically, the optic thalamus was practically normal except for a small portion where the tumor inpinged and caused a recent edema and cavitation with the fading-out of

cell structure. The edematous area extended as far as the anterior commissure. The convulsions, called autonomic by Penfield, were in his opinion caused by the tumor which periodically pressed on the optic thalami, causing irritation of some centers or conduction path in the thalamus "capable of setting into action the ganglia which exert control over vascular apparatus, sweat and tear glands, etc."

G. B. HASSIN.

PROLIFERATION OF THE ARACHNOID CELL IN AND AROUND THE DURA MATER. THOMAS WILLIAM BROCKBANK, Arch. Neurol. & Psychiat. **22**:444, 1929.

The presence in the dura of small nodular or vesicular outgrowths and their possible relationship to endothelioma have been studied by Brockbank in fifty-nine cases. The cases comprised patients of various ages, below 20 to 80, and also a variety of pathologic conditions such as tumors, meningitis, hydrocephalus, cerebral hemorrhage and eleven apparently normal persons. One gains the impression that the growths are proliferated arachnoid cells which form clusters "against" the dura and within the dura, and even force themselves through the latter. The growth has something to do with the increased intracranial pressure, but has little if anything to do with the age; as a matter of fact, it may occur in normal intracranial conditions, and the groups of the proliferating arachnoid cells may have characteristic whorls such as are found in endotheliomas.

G. B. HASSIN.

BLASTOMYCOTIC MENINGO-ENCEPHALITIS. ISTVÁN GÁSPÁR, Arch. Neurol. & Psychiat. **22**:475, 1929.

Blastomycosis usually appears as a cutaneous form and very seldom as a generalized form. In Gáspár's patient the cerebral meninges and the brain itself were involved—an extremely rare occurrence. The clinical symptoms were pain in the head and neck, tenderness over the occipital region, horizontal and vertical nystagmus, slight choking of the disks, some rigidity of the upper extremities and difficulty in walking. As a rule, the temperature was normal. The spinal fluid showed a marked increase in globulin, 35 cells per cubic millimeter and a pressure of 30 mm. of mercury. A ventriculogram was attempted but was unsuccessful. A subtemporal decompression gave a temporary improvement but two months later the patient developed difficulty in speech and convulsions. At a second operation an encapsulated growth was found over the rolandic area. It was firmly adherent to the dura and was 6.5 cm. in diameter and 2 cm. thick. Its internal layer infiltrated the brain tissue and was made up of miliary abscesses enveloped by connective tissue. Some fibroblasts grew among the leukocytes and were united with giant cells. The intermediate layer of the tumor contained numerous necrotic areas surrounded by hyaline connective tissue. This was abundant in the external layer of the tumor in which abscesses were absent. The microscopic diagnosis was chronic blastomycotic meningitis with formation of a large granulomatous mass. The blastomyces were well stained with the method of Levaditi. However, their presence is not necessary for differentiation from a tubercle, which the granulomatous mass resembles; it differs from a tubercle in the presence of abscesses and in the absence of the rampart of round cells around the focus which is common in a tubercle.

G. B. HASSIN.

THE ORIGIN OF OLIGODENDROGLIA IN CEREBRAL TUMORS. ARMANDO FERRARO, Arch. Neurol. & Psychiat. **22**:511, 1929.

The study of a pontocerebellar angle tumor, which looked like a neurinoma, macroscopically, showed it to be a mixed tumor of glial nature. Some areas were typical of spongioblastoma multiforme; ependymal cells predominated in some, and astrocytes in others. In addition, microglia cells predominated in some areas. Intermediary stages between normal cells and gitter cells could be well followed up, especially in areas undergoing degeneration. In some areas the microglia cells

exhibited the "pseudopodic" appearance which according to Hortega occurs in the immature stages of the microglia development. For such areas containing immature microglia cells, Ferraro would suggest the term microglioma. In other parts of the tumor oligodendroglia cells predominated, forming clusters; they were also scattered elsewhere. Some showed transitional stages in the form of astrocytes, a fact which reveals the common origin of these two types of cells. The oligodendroglia cells which Ferraro succeeded in staining were also scattered among the cells of the spongioblastic type. Careful study of transitional cell forms led Ferraro to the conclusion that "oligodendroglia cells are derived from a transformation of the secondary spongioblasts," that is, from the unipolar cell. He also found areas of spongioblasts coexistent with those of oligodendroglioma which in his opinion is a further argument that the oligodendroglia cells are derived from the spongioblasts.

G. B. HASSIN.

THE STRUCTURAL CHANGES FOLLOWING CEREBRAL TRAUMA. E. A. LINELL, Arch. Neurol. & Psychiat. **22**:926, 1929.

Linell repeated the experiments of Penfield with aseptic injuries to the brain. He studied the reactions of the glia produced for the purpose of ascertaining the functions of the various types of the supporting elements of the central nervous system. Since the work of Cajal and his school as such are recognized macroglia (fibrillary and cytoplasmic astrocytes), microglia (also known as Hortega cells) and oligodendroglia (generally known as glia nuclei). For these experiments a series of ten rabbits was used. The brain was injured through the insertion of an ordinary blunt probe from 1 to 3 cm. into the brain tissue or by insertion of a glass tube sharpened at the end and drawn out to a sufficiently fine caliber to pass through the burr holes. The rabbits were killed by chloroform at periods varying from three days to two months after the date of the brain wound. Fixation was in Cajal's formaldehyde bromide solution, and the staining methods were Penfield's modification of the Hortega's silver carbonate technic and other methods of the Cajal school. Reactive signs to the injury of the brain may show on the part of both the macroglia and microglia as early as the third day following the injury. The microglia has mainly a phagocytic function of scavenging the damaged tissue, especially the myelin. This activity reaches its maximum within about six days after the injury. The gradual transformation in so-called gitter cells can be followed up. The macroglia, however, showed its maximum reaction at three weeks, but its function is especially noticeable in late stages when it plays the principal rôle in formation of a brain scar tissue. At the end of two months the margin of the wounds is represented by a glial feltwork which begins at four weeks and a paucity of recognizable astrocyte cell bodies. The glial scar formed is the terminal result of the macroglia reaction.

G. B. HASSIN.

CHANGES IN THE SPINAL CORD IN ANEMIA. ARTHUR WEIL and CHARLES DAVISON, Arch. Neurol. & Psychiat. **22**:966, 1929.

Weil and Davison studied histologically the spinal cords in ten cases of pernicious anemia, seven cases of carcinomas of the stomach with secondary anemias, fourteen cases of various types of malignant conditions with secondary anemias, six cases of Hodgkin's disease with secondary anemia, three cases of lymphosarcoma with secondary anemia, six cases of tuberculosis with secondary anemia and four cases of leukemias. The purpose of the studies was to establish whether the changes in so-called subacute combined degeneration of the cord occur only in pernicious anemia or also in anemias associated with the foregoing states. For the various types of anemia the classification of Morawitz and Denecke was used, and that of Henneberg for the various types of changes in the spinal cord. In their material of seven cases of carcinoma of the stomach, only one showed neurologic signs of subacute combined degeneration of the cord, in spite of the presence in all of them of achlorhydria, a high color index and a duration of the disease of

from one to four years. Some of the cases of Hodgkin's disease showed clinical signs of subacute combined degeneration of the cord, but histologically one case showed a degeneration of the pyramidal tracts with Weil's hematoxylin stain, while in another case there was a slight involvement of Goll's columns. The cases of lymphatic and myelocytic leukemia showed no clinical or pathologic manifestations. Weil and Davison's conclusion is that the current opinion that all types of anemias may cause subacute combined degeneration of the cord should be modified. The etiology should be limited to hemolytic anemia, especially to the progressive pernicious form and, in rare cases, also to hemolytic anemia from other causes; for example, that caused by infestation with *Bothriocephalus latus*.

G. B. HASSIN.

OCULAR DISTURBANCES IN EPIDEMIC ENCEPHALITIS. F. KENNEDY, Arch. Ophth. **1**:346, 1929.

Forcible spasmotic shutting of the eyes may occur. This belongs in the same category of release phenomena as spasmotic torticollis. Ptosis of the eyelids is a frequent symptom of encephalitis and is often found in association with weakness or paralysis of both external recti. Blepharospasm also occurs and is due to involvement of the third nerve or nucleus.

Transient diplopia, usually unaccompanied by strabismus is perhaps the most frequent single diagnostic feature of the early stages of encephalitis.

There is apt to be a special lymphocytic infiltration in the region of the quadrigeminal plate, near or in the oculomotor nuclei. This produces the Parinaud syndrome (a diminution or loss of conjugate associated movements of the eyeballs upward or downward). These disturbances occur with sudden onset commonly in the acute stages of the disease but may be slowly progressive in chronic cases. In the latter there is a widespread neurogliar proliferation and degeneration of vascular walls with numerous thrombi and small hemorrhages.

The subependymal, peri-aqueductal changes are the cause of the not rare appearance of an Argyll Robertson pupil in encephalitis. One may also find paresis of accommodation which is usually bilateral. Nystagmus is almost the rule in acute encephalitis, both the cerebellar and labyrinthine varieties. True retrobulbar neuritis is rare; papilledema is not common. Optic neuritis occurs late in the disease and is due to sudden blocking of interventricular drainage by meningitic exudate.

CHARLES WEISS.

PYELITIS, URETERITIS AND CYSTITIS CYSTICA. J. J. JOELSON, Arch. Surg. **18**:1570, 1929.

The author reports a case of this interesting lesion of the urinary tract which was bilateral and which was associated with nephrolithiasis. The diagnosis was made by ureterograms and pyelograms.

N. ENZER.

TRAUMATIC ARTHRITIS: HISTOLOGIC CHANGES IN HYALINE CARTILAGE. M. N. SMITH-PETERSEN, Arch. Surg. **18**:1216, 1929.

From a comparison of sections of the sacro-iliac joints in normal persons with those from patients having a history of recurring strain in this joint, one finds that the hyaline cartilage undergoes a cycle of changes beginning with a surface fibrosis which later shows a myxedematous degeneration. This in turn is invaded by fibrous tissue replacing the matrix, and, finally, calcification.

N. ENZER.

INTRACRANIAL SARCOMATOSIS OF LEPTOMENINGEAL ORIGIN. PERCIVAL BAILEY, Arch. Surg. **18**:1359, 1929.

The reviewer may perhaps be excused for a little more than ordinary enthusiasm over this article. It is a scholarly review which embraces the investi-

gations concerning the embryology of the meninges and the origin of a series of rather rare tumors. Bailey points out that a great deal of the evidence points to the leptomeninges as having a neuro-epidermal origin. Nevertheless, the fact that there are tumors having a fibroblastic structure makes their histogenetic classification somewhat difficult, and he warns against a too schematic consideration of these structures. The advisability of the use of the term sarcoma may be in question, but the fact that they do differ from other intracranial tumors of neuro-epidermal origin supports the use of this term, especially from a descriptive standpoint. The first group he described consisted of several peritheliomas. These tumors characteristically spread over the meninges to form a so-called sarcomatosis or endotheliomatosis, and all of them have occurred in adults after the age of 30. On the other hand, a similarly invading tumor of nerve tissue origin almost always occurs in children, and these are composed of a peculiar type of cell from which Bailey and Cushing have called these tumors medulloblastomas. The microscopic appearance of these tumors is characteristic from several standpoints: first, the characteristic perivascular layer of cells, and the fact that these cells form a reticulum. The tumor grows in these perivascular arrangements, and may arise spontaneously from several foci. In its advancement it leaves a shell of sclerotic brain tissue between the islands, and intervascular characteristic areas of necrosis occur, which is different from the small cell medulloblastoma. He described a similar tumor which probably took origin from the leptomeninges and encroached on the brain tissue without invading it. Of a group of perithelial sarcomas he describes two in which the cells are more nearly spherical, and which also show a similar characteristic reticulum. Mitotic figures here are numerous, and the tumor is more malignant. Fibroblastomas are included for consideration, and in these there is a dense, spindle cell structure. An alveolar sarcoma is described in which the reticulum is of especial importance, and a distinguishing feature between the medulloblastomas and neuro-epitheliomas as opposed to sarcomas is the fact that the nuclei of the reticulum cells are particularly prominent in the former. In discussing the tumors which have melanotic cells in them, he points out that this might be strong evidence of a neuro-epidermal origin, but at the same time a dopa reaction has not been obtained from them. The article is extremely well illustrated, and an abstract could hardly do it justice. The study of these rare tumors is mainly interesting from the standpoint of theoretical pathology, but nevertheless may be useful in the study of the embryology of the leptomeninges.

N. Enzer.

Elastic Tissue in Meningeal Fibroblastomas: So-Called Dural Endotheliomas. W. P. Van Wagenen, Arch. Surg. **18**:1621, 1929.

This article is illustrated with sections from a tumor of a fairly dense cellular structure, in which elastic tissue fibrils were demonstrated. These fibrils were found some distance from the dura, and from their abundance the author feels that they were not derived from the stroma. They were closely related to the tumor cells. Also, he observed that fibroglia fibrils were fused together into elastic tissue fibrils. He agrees with Penfield in the terminology of meningeal fibroblastoma as opposed to endothelioma.

N. Enzer.

Branchial Apparatus. O. R. Hyndman and G. Light, Arch. Surg. **19**:410, 1929.

This is an extensive review of the history, anatomy and embryology of the branchial areas, and an analysis of cysts and fistulas, with a differential diagnosis and a description of the pathologic process. A table of sixty-one cases selected from the literature is included. The authors feel that these anomalies are due to ectodermal and entodermal epithelial inclusions. There is a tendency to familial

occurrence, transmission being through the maternal side. They offer a simple classification of branchial cleft epidermoid cysts and branchial cleft mucous cysts.

N. ENZER.

LYMPHATIC DRAINAGE FROM THE PERITONEAL CAVITY IN THE DOG. G. M. HIGGINS and A. S. GRAHAM, Arch. Surg. **19**:453, 1929.

The authors used a method of graphite injection into the peritoneal cavity, and studied the lymphatics in the upper peritoneal areas and on the surface of the diaphragm. From their observations they conclude that the removal of graphite in the dog is largely through the diaphragmatic lymphatics and the sternal branches. The pigment appears in the sternal lymphatic channels long before it does in the thoracic duct. They do not feel that the thoracic duct plays an important part in lymphatic drainage of the peritoneal cavity. The infected pigment appears in the lymph nodes at the upper portion of the chest wall relatively early, and is both intracellular and lying free, whereas in the thoracic duct, when it does appear, it is nearly always extracellular. From an hour to an hour and a half elapsed before the graphite was found in the thoracic duct, whereas it appeared very early in the sternal lymph channels. The cells in the thoracic duct which did contain graphite were similar to the cells found in the peritoneal cavity.

N. ENZER.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE. L. R. WHARTON and F. H. KROCK, Arch. Surg. **19**:848, 1929.

The authors claim that there are about 230 cases of this lesion on record, and they now present a review of 14. The relationship of salpingitis is commented on. It probably does not bear an important etiologic relationship to the onset of malignancy, and it is difficult sometimes to determine whether the inflammatory reaction found at the time of operation is primary or secondary to the tumor growth. The dissemination of the tumor depends largely on whether or not the fimbriated end will be closed. If it is not, the tumor is early implanted into the peritoneum. The tumor arises in the mucous membrane, and may give rise to a papillary or alveolar growth, or combinations of both of these. In some instances one finds a papillary hyperplasia of the tube in which the cells do not appear to be malignant, and yet the structure is that of a malignancy. Finally, these papillae may show malignant change. The growth is usually inward toward the lumen of the tube, and finally the mass fills and distends the tube before invasion of the muscularis occurs. Often bilateral metastases occur early and are widespread.

N. ENZER.

LEUKOPLAKIA OF THE RENAL PELVIS. A. A. KUTZMANN, Arch. Surg. **19**:871, 1929.

Including the author's case, sixty-seven cases of this lesion of the renal pelvis are on record. This article includes a tabular summary. The etiology is unknown, and is most frequently discovered after the kidney has been removed for some other lesion, especially infections, or stone. One of the important phases of the study of this condition is its relationship to malignancies of the renal pelvis, and of the sixty-seven cases 11.9 per cent contained carcinomas, seven of which were squamous cell. The appearance of the leukoplakia in the renal pelvis is apparently not different from leukoplakic patches elsewhere. The lesions present the characteristic layers of squamous epithelium, except that cornification is not completely developed. Several variations in degree of differentiation are recognized. The most likely theory accounting for this condition is that of metaplasia under the influence of some chronic irritation. It is most common in the fourth decade, does not give any characteristic clinical signs, and occurs as frequently in the right or the left kidney, and in both sexes.

N. ENZER.

GROSS AND MICROSCOPIC STRUCTURE OF THE THYROID GLAND IN MAN. W. F. RIENHOFF, JR., Arch. Surg. **19**:986, 1929.

This is a most interesting study of the anatomy of the thyroid gland. The method used was the study of large pieces of the gland by wax plate reconstruction and by maceration and microdissection. A lengthy description is given of the technic. The observations that Rienhoff obtained point to there being definite independence of the thyroid acini, that they do not merge into others, that there is no true lobulation of the thyroid gland and that the acini vary in size under normal conditions and still more in hyperplastic states. There is marked variation in the architecture of the gland from field to field, as demonstrated in his illustrations. The article is extremely difficult to abstract, and must be read to appreciate the nature of the work and the extent to which it was carried. The interesting outcome of this work is the fact that there was no demonstration in any of his sections or plates of fetal rests as described by Wolfler.

N. ENZER.

CHRONIC COPPER POISONING. CYRIL J. POLSON, Brit. J. Exper. Path. **10**:241, 1929.

Experiments are reported which are considered to be a fair repetition of the experiments of Mallory, Parker and Nye, in which they believe that they had produced an accumulation of iron-free pigment in the liver and cirrhosis of the organ, following administration of copper acetate. They considered this pigment allied to hemofuscin. Polson finds, however, that copper acetate fails to produce a higher incidence of pigment cirrhosis in the liver than is found in normal controls when all of the rabbits are fed on cabbage, oats, bran and thirds. However, in a series of control rabbits fed on a diet containing mangel-wurzels and turnips there is an accumulation of "hemofuscin" in the livers of 87.5 per cent of the rabbits.

J. N. PATTERSON.

INFLUENCE OF LOCAL METABOLIC PROCESSES ON THE REACTIVE AND REGENERATIVE PHENOMENA OF INFLAMMATION. E. LEUPOLD, Beitr. z. path. Anat. u. z. allg. Path. **81**:45, 1928.

In the newer conceptions of the nature of inflammation, physiologic and chemical factors receive greater attention than the causative and teleologic phenomena emphasized in the older views of the process. Leupold studied experimentally the effects of chemicals on the reparative and regenerative reactions in inflammation. The chemicals the effects of which were to be studied were dropped several times daily into small incisions made into the skin of white mice. After two or three days, when the wound had closed, the chemicals were injected in 0.5 cc. amounts into the skin about the healing wound. The tissues were examined microscopically at varying intervals during from three to ten days after the incision was made. The substances used were such as might be conceived to take part in the local normal metabolism: proteins (albumin, globulin, casein), peptone, amino-acids, urea and ammonium carbamate; fats and their derivatives, as olive and linseed oil, soaps, glycerin, fatty acids; the carbohydrates, glycogen and dextrose; salts (sodium chloride, carbonate and bicarbonate, potassium chloride, magnesium phosphate, sodium and potassium phosphate). These substances were used in varying dilutions of from 1 to 0.0001 per cent. The mineral salts, through their physicochemical properties in the presence of living tissues, more especially through their buffer action and their effect on the H-ion concentration, act as stimuli to cell and tissue proliferation. The organic substances of large molecular structure, namely, the proteins, fats and carbohydrates, through such effects as they may have on H-ion concentration, surface tension and nutrition of the living cells, also cause increased cell proliferation and more rapid regeneration. Such influence in the case of the proteins is dependent on optimum physicochemical conditions brought about by the salts. The oils used caused increased proliferation of epithelium and of lymphatic endothelium, even in the absence of any salt action.

O. T. SCHULTZ.

REGRESSIVE CHANGES IN NORMAL COSTAL CARTILAGE. R. BÖHMIG, Beitr. z. path. Anat. u. z. allg. Path. **81**:172, 1928.

Böhmig reports the results of a gross and microscopic study of costal cartilages obtained from the necropsy service of Schmorl's institute. The age ranged from less than 1 to more than 80 years. The gross examination was based on 484 cases, the microscopic on 301. For microscopic study, the first, third, fifth and seventh costal cartilages were taken. The study was limited to regressive, or perhaps degenerative changes, which may be considered to fall within the range of normal alterations, inflammatory and neoplastic reactions being excluded. Beginning at puberty there occurs a progressive relative increase in ground substance, at the cost of the cellular elements. A decrease in the number of penetrating blood vessels begins in childhood and is due to local nutritional degenerative changes in the perivascular connective tissue. Loss of vascularity is associated with asbestos-like fibrillation of the ground substance and with the formation of cleftlike spaces in the latter. The fibrillation occurs about the blood vessels, the fibrils being arranged at right angles to the latter, and in the subperichondrial growth zone. Medullary spaces, traversed by a meshwork of fibrils, are formed within the substance of the cartilage; the fibrils are the collagenous fibrils of the original ground substance. True ossification was noted more frequently than simple calcification. Except in the first rib, ossification occurs irregularly within the cartilage, and begins in the areas of fibrillation and medullary space formation, usually with the formation first of a fatty marrow. The formation of bone is secondary to the formation of the fatty marrow. The perichondrium takes no part in bone formation. Subperichondrial proliferation of cartilage cells was seen at all ages. Böhmig considers the changes noted by him as primarily degenerative and dependent on nutritional changes brought about by the normal disappearance of blood vessels with age. The primary degenerative changes about the blood vessels are regularly followed by regenerative changes, such as formation of fibrils, fibrillated marrow and bone. The latter changes the author considers cataplastic in nature.

O. T. SCHULTZ.

MALDEVELOPMENT OF UROGENITAL TRACT. C. VAN GELDEREN, Beitr. z. path. Anat. u. z. allg. Path. **81**:213, 1928.

The author reports briefly two examples of urogenital malformation. The first, in a woman aged 23, consisted of absence of the right kidney and ureter, a symmetrically bicornate duplex uterus, an incompletely septate vagina and persistence of the left inferior vena cava. In the second case, that of a girl aged 17 years, the left kidney and ureter were absent, the uterus was bicornate and duplex and the vagina was subdivided by a complete septum.

O. T. SCHULTZ.

ADENOMA, PSEUDO-ADENOMA, AND MASTOMA OF MAMMARY GLAND. P. PRYM, Beitr. z. path. Anat. u. z. allg. Path. **81**:221, 1928.

By means of detailed descriptions of selected cases, richly illustrated with pictures in the text, Prym attempts to elucidate the differences between true adenomas of the female breast and areas of nonblastomatous hyperplasia. Such areas occur as nodules of variable size and are fairly well circumscribed in the gross, but are not encapsulated or readily shelled out, as are the adenomas. Such pseudo-adenomas arise as localized areas of hyperplasia in normally differentiated mammary tissue, probably as the result of hormonal stimuli. Evidences of their nonblastomatous character are their closer relation to the surrounding tissue, the relationship of their duct system to that of adjacent tissue and more marked reactive changes in their blood vessels. The most important differential point is the presence within the pseudo-adenoma of adipose tissue, which, according to Prym, never occurs in the true adenoma unless secondarily drawn into the nodule at the periphery. Pseudo-adenomas may show the same regressive

changes as those present in the breast from which they come. The small non-encapsulated nodules, so frequently seen in the mammary gland, and which are usually described as adenomas and presented as evidence that the adenoma may arise from normal completely differentiated mammary tissue, are not true adenomas but pseudo-adenomas. The true adenomas may be arranged in a series which includes at one extreme tumors with actively proliferating ducts, acini and lobules, and at the other extreme completely differentiated tissue with a lobular arrangement, which tissue closely simulates that of the mammary gland. Prym terms such completely differentiated adenomas mastomas, but emphasizes that he applies the term mastoma to circumscribed tumors and not to the diffuse adenomatous proliferation of the entire gland, as was done by Schminke. The intracanalicular fibro-adenoma, for which Prym prefers the descriptive name Spaltenadenom or fissure adenoma, also shows the same gradation of changes from active proliferation to complete differentiation. Prym considers it important from both the clinical and the statistical point of view to distinguish between adenoma and pseudo-adenoma.

O. T. Schultz.

Quantitative and Qualitative Morphologic Reactions of the Suprarenal Glands of the Guinea-Pig to Certain Stimulants. R. Kojima, Beitr. z. path. Anat. u. z. allg. Path. **81**:264, 1928.

In order to evaluate the changes caused by amanita toxin in the suprarenal glands of the guinea-pig, Kojima studied these glands in normal and starved animals and in a small number of animals subjected to ether narcosis and to the injection of gelatin solution into the abdominal wall. He paid particular attention to the size of the organs in relation to the body weight, to the relative proportions of medulla and cortex, to the relative thickness of the layers of the cortex, and to the microchemical reactions of the cells. The left suprarenal gland is normally larger than the right, and the relation of the total weight of the organs to the total body weight is as 1 to 5,405. In starved animals the weight is absolutely and relatively increased, the relation to the body weight being at 1 to 2,607. In the starved animal the zona glomerulosa is decreased in thickness, the zona reticularis increased. The capillary endothelium of the normal cortex contains yellowish pigment; this is increased in pregnant and in starved animals. Much iron-containing pigment is present in the parenchymal cells of the cortex, especially those of the zona reticularis; this is greatly increased in starving animals. Neutral fat is present normally in the zona glomerulosa and the zona reticularis. Anisotropic lipoid material is not normally present in the cells of the zona glomerulosa and zona reticularis, but is present in large amount in the middle portion of the zona fasicularis. Anisotropic lipoids are decreased in the suprarenal glands of starved animals; isotropic lipoids may be either increased or decreased. In normal pregnant animals the quantitative relationships of the lipoids are identical with those of normal animals. Nuclear fragmentation and nuclear division occur normally in the zona glomerulosa and in the outer portion of the zona fasicularis. In starvation, degenerative changes are noted in the cortical cells, and the cortex is hyperemic. The cells of the medulla of starved animals contain hyaline droplets; the chromaffin content is not altered in starvation. In the small series of animals subjected to damage by ether or injection of gelatin, the cortex was increased in thickness after from three to six days, the increase being chiefly of the zona reticularis. Brownish pigment was greatly increased in amount in the endothelial cells and in the cells of the zona reticularis.

O. T. Schultz.

Histology of Venereal Granuloma. W. Fischer and K. von Gusmar, Beitr. z. path. Anat. u. z. allg. Path. **81**:309, 1928-1929.

The authors give a condensed summary of the pathologic histology of venereal granuloma, based on a study of material from fifty-two cases. Most characteristic is the parallel course of the numerous newly formed blood vessels perpendicular to the floor of the ulcer. The latter is covered by a layer of fibrin

which contains leukocytes. Each vessel is surrounded by a thick mantel of young cells. The predominating cell type is the plasma cell. Lymphocytes, polymorphonuclear leukocytes, eosinophil leukocytes and mast cells also occur, but are much less numerous than the plasma cells. In the granulation tissue are large mononuclear histiocytes which contain the specific organism; these cells show various degenerative changes. The authors consider the histologic observations characteristic enough to permit making the specific diagnosis, but believe that the diagnosis must rest on the whole microscopic picture rather than on any single element. They emphasize the proliferative reaction of the epithelium at the margin of the ulcer; this is often so marked and atypical as to suggest epithelioma. The specific relation of the organism and its biologic characters are briefly discussed.

O. T. SCHULTZ.

EXPERIMENTAL STUDY OF THE INTERSTITIAL CELLS OF THE TESTIS. E. J. KRAUS, Beitr. z. path. Anat. u. z. allg. Path. **81**:323, 1928.

Kraus presents the results of work done five years previous to its present publication. In the interval, much similar experimentation has been published. The work consists of a histologic study of the testis of the cat, with especial attention to the interstitial cells, after a variety of experimental procedures. The latter included roentgen irradiation, transposition of the testis into the peritoneal cavity, transplantation into the lower abdominal wall, successive partial resections of the testis and ligation of the vas or epididymis, these various procedures being followed in some animals by roentgen irradiation. The work was done on young, sexually immature animals, and on older, sexually mature ones. In young animals, the various procedures caused a decrease of both tubular elements and interstitial cells. When such animals reached sexual maturity, provided the germinal cells of the tubules were not completely destroyed, the interstitial cells increased in number at this time. In older animals, the procedures caused relative and absolute increase in the number of interstitial cells, which became most marked after the degenerative changes in the tubular epithelium had passed their maximum, and at a time when proliferation of the most undifferentiated tubular cells was most active. Kraus compares the appearances at this stage with those which precede a period of sexual activity in the species of animals characterized by intermittent periods of sexual activity separated by long inactive intervals. Ligation of the vas or epididymis did not cause an increase in the number of interstitial cells. Reduction of the amount of testicular tissue, by removal of one testis or successive resections, following the various procedures, increased the degree of interstitial cell hypertrophy and hyperplasia. In all the experiments, an essential for proliferation of the interstitial cells was the persistence of viable, undifferentiated germinal cells within the tubules. From his own work and that previously published, Kraus concludes that the interstitial tissue is not an endocrine organ in the sense of Steinach and various other writers; it is not the "organ of manhood," on whose normal functioning the development of the normal secondary sexual characteristics depends. A resorptive function is also denied. The primary function of the interstitial tissue is trophic, the furnishing of necessary specific substances to the germinal epithelium. The transfer of such substances is not a direct one, as has been postulated by some, but occurs by way of the local circulation. In addition to its trophic function, the interstitial tissue also has internal secretory activity, but only in relation to spermatogenesis. In its endocrine activity the tissue is probably correlated in function with the hypophysis or midbrain. The other endocrine organs showed no characteristic changes in the animals studied by Kraus.

O. T. SCHULTZ.

EFFECT OF ROENTGEN IRRADIATION ON RETICULO-ENDOTHELIAL PHAGOCYTOSIS. MARIA SCHWIENHORST, Beitr. z. path. Anat. u. z. allg. Path. **81**:375, 1928.

The effect of roentgen irradiation on the phagocytic activity of the reticulo-endothelial system of the spleen, liver and lung was studied in white rats. The

animals were subjected to varying doses of filtered or unfiltered roentgen rays; the details of the roentgen technic are not given. Irradiation was followed by the injection into the femoral vein of a suspension of staphylococci heated to 60 C. for one hour. The injection followed the irradiation immediately or at intervals of three and six hours, and one, two and three days. The animals were killed for examination immediately after the injection, or at intervals of five, fifteen and forty minutes, two and three hours, and one, two and three days. In one series of experiments injection of the bacteria preceded the irradiation. In control animals, the sinus endothelium of the spleen, the Kupfer and endothelial cells of the liver, and the septal cells of the lung, as well as the polymorphonuclear leukocytes throughout the body exhibited active phagocytosis of the injected cocci, which disappeared rapidly from the blood stream. In injections made up to three hours after radiation, no definite effect on phagocytosis could be detected, although morphologic cellular changes were already evident. The earliest change noted occurred in the spleen and consisted of pyknosis and fragmentation of the lymphocytes. At three hours the lymphoid follicles of the spleen were decreased in size and the reticulo-endothelial cells of the organs examined were swollen. At six hours the capillaries throughout the body were filled with leukocytes in a state of active phagocytosis. When the injection was made at intervals longer than six hours after irradiation the degree of cellular damage was greater, phagocytosis was much less marked, and cocci remained in the blood stream for much longer periods than in controls. Animals allowed to live after roentgenization and injection of organisms did not live as long as controls subjected to bacterial injection alone. In the former, clumps of nonphagocytosed cocci could be seen in the capillaries. The author concludes from her experiments that irradiation damages the cells of the reticulo-endothelial system and decreases or destroys their phagocytic activity. There was no evidence of increased formation of agglutinins or bacteriolysins, as has been claimed by some writers. An apparent slight stimulating effect of the roentgen rays occurs at the six hour period, when leukocytosis is at its height. The temporary, slightly increased antibacterial activity of the body tissues and fluids at this stage is due to the leukocytosis and to the liberation of preformed antibacterial substances from cells injured by the rays. The beneficial clinical effect which may follow irradiation of a localized area of inflammation is due to the same factors.

O. T. SCHULTZ.

EXPERIMENTAL ACUTE PEPTIC ULCER. F. BÜCHNER, P. SIEBERT and P. J. MOLLOY, Beitr. z. path. Anat. u. z. allg. Path. **81**:391, 1928.

The generally accepted view that the acute peptic ulcer is the result of digestion of areas of gastric tissue which have been killed by infarction, the latter being due to disease or spasm of the blood vessels or to spasm of the gastric or duodenal muscle wall, has been opposed by Aschoff. He has maintained that the histology of the acute gastric or duodenal ulcer, as seen in the human being, is not that of tissue which has been infarcted and has died and then undergone digestion. He claimed that it is living tissue which is acted on by the gastric juice and that the reaction is an acute inflammatory one. The harmful action of the gastric juice is not necessarily due to abnormal composition of the fluid, but to disturbance of what Aschoff has termed the normal correlation between gastric juice and gastric wall. This correlation may be disturbed not only by changes in the gastric juice, but also by changes in the gastric wall other than infarction or spasm. The present work, from Aschoff's institute, deals with the experimental production of acute ulcers in the stomach of the rat by means of histamine, the latter being an agent which disturbs the normal gastric juice-gastric wall correlation by leading to the formation of an increased amount of gastric juice of increased acidity. The hypersecretory action of histamine is held to be due to an action directly on the secretory cells. In a series of acute experiments, rats that had been starved for twenty-four hours received one or two subcutaneous injections of histamine in a dosage of 0.06 Gm. per hundred grams of body weight. Acute

ulcers were found in 33 per cent of the animals, as compared with 6 per cent in animals that did not receive histamine. In another series, a hunger day during which the animals received one or two injections of histamine was alternated with a day during which the animal was allowed to eat, the duration of the experiment being seventeen days. In this series, acute ulcers were found in 80 per cent of the animals receiving two daily injections of histamine, in 60 per cent of those receiving a single daily injection and in 40 per cent of those merely subjected to starvation every alternate day. The ulcers were most often multiple, and occurred only in the proventriculus, that portion of the stomach devoid of secreting cells and lined by squamous epithelium. This portion of the rat's stomach, termed the work portion in contradistinction to the secreting portion, is likened to the antral portion of the human stomach with its alkaline secretion. The histologic changes were those of necrosis brought about by the caustic action of the gastric juice and acute inflammation. The authors insist that the lesions could not have arisen as the result of infarction. Action of histamine on the blood vessels, the gastric musculature or the vegetative nervous system is excluded by the authors.

O. T. Schultz.

Vascular Observations in Lupus Vulgaris. S. Bettmann, Beitr. z. Klin. d. Tuberk. **72**:208, 1929.

Capillaries in the margins of lupus play a conspicuous rôle in the healing process. This fact is well illustrated by capillary photography on the living. This type of observation aids in establishing the diagnosis and in assaying the value of therapeutic measures.

Max Pinner.

Fatal Hemorrhage from a Traction Diverticulum of the Esophagus and Perforated Bronchus. J. Heine, Deutsche med. Wchnschr. **55**:1135, 1929.

A Chinaman, aged 35, died after repeated massive hemorrhages apparently from the lungs. At postmortem examination, a cavity in a mass of tuberculous tracheobronchial lymph nodes was found opening into a traction diverticulum of the esophagus and into the left main bronchus just below the bifurcation of the trachea. A bronchial artery was eroded with massive hemorrhage into the lungs and bowel. (See the report by E. O. Latimer and J. D. Willems. Chicken-Bone Perforation of the Esophagus with Bacterial Erosion of the Left Bronchial Artery, Arch. Path. **6**:426 [Sept.] 1928.)

Paul J. Breslich.

Lipoid Nephrosis. O. Diebold, Deutsche med. Wchnschr. **55**:1550, 1929.

The urine of a girl, aged 24, who died of cardiac decompensation, was found to contain globules of fat, large amounts of albumin and hyaline and granular casts. In the blood there were 390 mg. of cholesterol and 47.6 mg. of nonprotein nitrogen per hundred cubic centimeters. The serum albumin was decreased while the globulin was increased. The blood pressure was 150 systolic and 95 diastolic. At postmortem examination, the kidneys each weighed about 300 Gm., and the capsules stripped easily from a smooth yellow surface. On surfaces made by cutting the kidneys, the cortex was widened and the tissue was yellowish gray with a cloudy swelling. There were no marked changes of the medulla. Histologically, there were large amounts of lipoid substance in fine droplets in the cells lining the tubules in the cortex of the kidney and deposits of fat in the glomeruli which were otherwise unchanged. A marked increase of fat was also noted in the cells of the liver, suprarenal glands, hypophysis and myocardium and in the ovary. The author believes that the changes in the kidney in lipoid nephrosis are only part of a generalized disturbance of fat metabolism which involves all tissues.

Paul J. Breslich.

EXPERIMENTAL STUDIES OF THE REACTION OF THE LYMPHATIC APPARATUS OF THE SPLEEN DURING HUNGER, HEMORRHAGE AND INFECTION. H. GROLL, Verhandl. d. deutsch. path. Gesellsch. **24**:10, 1929.

The experiments permitted of the following deductions: Extirpation of the lower pole of the spleen produced no histologic alteration in the remainder of the organ. Hypertrophy of the splenic follicles occurred one day after infection of the body. After hemorrhage, there was a marked proliferation and development of the lymph nodes. The spleen possesses definite lymph centers which are not reaction centers, but epithelioid centers which are apparently degenerated lymph centers.

GEORGE RUKSTINAT.

AN UNUSUAL GRANULOMA OF THE NOSE, THROAT AND MOUTH. E. J. KRAUS, Verhandl. d. deutsch. path. Gesellsch. **24**:43, 1929.

The disease was noted in a blacksmith, aged 60, a horseshoer, aged 30, and a tobacco packer, aged 33. Grossly, the lesion was thickened, had a sloping edge and a granulated, speckled, grayish-yellow floor and resulted in death of the host in from five and one-half to twenty-three months. Histologically, the lesion was composed of granulation tissue, small epithelioid cells, giant cells and round and plasma cells. Bacteriologically, no specific organism was demonstrable. Death was due to hemorrhage from the necrotic granuloma.

GEORGE RUKSTINAT.

SPONTANEOUS FAT GRANULOMA. A. J. ABRIKOSSOFF, Verhandl. d. deutsch. path. Gesellsch. **24**:57, 1929.

Localized necroses in the subcutaneous fat are recorded in death from practically all causes. The author recognizes four types: that occurring after the subcutaneous injection of oily medicaments; a traumatic type; a type occurring at the periphery of inflammatory processes, and a spontaneous fat granuloma due to ischemia. Various things may occur in these granulomas. They may become conglomerate forming tubercle-like structures and then undergo fibrous transformation. At times they change into serous cysts or masses of scar tissue. Some become partially calcified and have fibrous borders while others become totally calcified.

GEORGE RUKSTINAT.

THE REACTION IN THE NEIGHBORHOOD OF MALIGNANT GROWTHS. W. FISCHER, Verhandl. d. deutsch. path. Gesellsch. **24**:263, 1929.

Fischer concludes that there is nothing specific in the inflammatory reaction surrounding malignant growths.

GEORGE RUKSTINAT.

THROMBOPENIC PURPURA. OLGA BYKOWA, Virchows Arch. f. path. Anat. **268**:606, 1928.

From the anatomic study of two cases, the author concludes that essential thrombopenia is not purely a lesion of megakaryocytes but one affecting the entire blood-forming and blood vascular systems. Essential thrombopenia and aleukia hemorrhagica are related conditions. A megakaryotoxicosis exists in both conditions but with the remaining primitive cells of the bone-marrow also affected.

V. C. JACOBSEN.

THE HEALING OF INCISED WOUNDS OF THE SKIN IN FISH. RUDOLF HARABATH, Virchows Arch. f. path. Anat. **268**:794, 1928.

This is an experimental study of the healing of incised wounds of fish, *Cobitis fossilis*, *Trutta fario* and *Anguilla vulgaris* being used in the investigation. The time intervals were from thirty minutes to six months. It was found that epithelial

repair of skin wounds occurs more quickly than in warm-blooded animals, but with a delay, however, in the formation of the "cell knobs." The basal layer of the wound consists of fibrin. The defect in the cutis becomes filled with new cicatricial tissue, the subcutaneous and interstitial connective tissues participating. Mitosis in epithelial or connective tissue cells was not observed. Fish are insensitive to incised wounds. A simple incised wound or an incised wound with loss of substance shows a tendency to infection either with fungus spores or with bacteria.

V. C. JACOBSEN.

CROSSED EMBOLISM IN PERSISTENT FORAMEN OVALE. A. WINKELBAUER and K. URBAN, Wien. klin. Wchnschr. **42**:1072, 1929.

If pulmonary embolism occurs in the presence of an open foramen ovale, an overflow into the arterial system usually takes place at the same time. In such cases the left brachial artery and the anonyma are involved with special frequency. Even small thrombi that ordinarily would cause comparatively slight symptoms on the part of the lungs may call forth in that way severe manifestations, particularly on the part of the brain.

AUTHORS' SUMMARY.

Pathologic Chemistry and Physics

LIPID STUDIES IN XANTHOMA. U. J. WILE, H. C. ECKSTEIN and A. C. CURTIS, Arch. Dermat. & Syph. **20**:489, 1929.

Chemical analysis of additional xanthomatous tumors confirmed the previously reported results that only from 1.5 to 2 per cent of the total lipid content of these tumors is cholesterol. The case of a diabetic patient in whom xanthomatous lesions appeared and disappeared by manipulations of the diet is described. In addition, xanthomatous lesions occurring with symmetrical distribution in sisters are reported.

FRANK M. COCHEMS.

RENAL INSUFFICIENCY WITH BENCE-JONES PROTEINURIA. EDWIN G. BANNICK and CARL H. GREENE, Arch. Int. Med. **44**:486, 1929.

The urine should be examined for Bence-Jones protein in all patients with renal insufficiency and when marked proteinuria exists, especially when associated with anemia. If this is done many cases of Bence-Jones proteinuria now overlooked may be recognized.

THE EFFECT OF CATHODE RAYS ON THE PROTEINS OF SERUM. LILLIAN E. BAKER and ROBERT B. COREY, J. Exper. Med. **50**:439, 1929.

The effects of cathode rays on the proteins of serum appear to be denaturation of a large proportion of the albumin and globulin with the formation of products that are soluble at the p_H of the serum; the production of a tough and exceedingly insoluble substance on the window of the cell where most of the absorption of electrons occurs; a slight hydrolytic cleavage of the protein molecule producing a small quantity of products having properties so near to those of the protein that they are precipitated by trichloracetic acid but are not removed by coagulation at the iso-electric point; the production of a small amount of hydrolytic products not precipitated by trichloracetic acid; and the formation of a small amount of ammonia, part of which at least is derived from the urea in the serum. It is interesting to note that these changes are such as would bring about exactly those effects on fibroblasts which were observed when cultures were grown in serum which had been subjected to cathode ray irradiation. The proteins of serum have a retarding effect on the growth of fibroblasts. One might therefore expect their removal by denaturation and coagulation to result in the slightly larger growth which was observed. The production of SH groups in the denatured protein

molecule would also tend to have a beneficial effect, as has been observed in experiments with denatured albumin. A concentration of protein split products equal to that in the irradiated serums has been observed to produce cells of characteristic appearance, full of cytoplasmic granulations and possessing long, active pseudopods, such as those noted in colonies cultivated in serum which had been subjected to cathode rays.

AUTHORS' SUMMARY.

THE RÔLE OF ENZYME ACTION IN THE FORMATION OF DENTAL CALCULI. KENNETH T. ADAMSON, Australian J. Exper. Biol. & M. Sc. **6**:215, 1929.

An active enzyme which is capable of hydrolizing glycerophosphoric ester is contained in the human gum tissue and in the oral tissue of the dog. In the saliva and blood serum there are phosphate-containing complexes (probably in the nature of phosphoric esters) which are capable of being hydrolyzed by the enzyme. The interaction of the enzyme on these phosphate-containing complexes results in the liberation and deposition of free inorganic phosphate. Under favorable conditions the liberated inorganic phosphate will form concretions. The action of the enzyme (liberated by trauma) on the saliva may thus give rise to salivary calculus. The increase in free phosphate in saliva, accompanied by an increase in the copper-reducing power, on hydrolysis with 0-1 N acid points to the fact that the organic phosphate is in the nature of a phosphoric ester, probably of the hexosephosphoric group. Human oral gum tissue does not contain pyrophosphatase in any estimable quantity.

AUTHOR'S SUMMARY.

SOLUBLE SULPHUR COMPOUNDS IN THE ERYTHROCYTES. E. GABBE, Klin. Wchnschr. **8**:2077, 1929.

A method was described for determining the sulphhydril compounds of the blood, glutathione and thionine, which is based on the oxidation of the SH group with potassium ferrocyanide in acid medium. By this method, from 24 to 46 mg. per hundred cubic centimeters of normal blood was found, calculated as glutathione, which was contained in the erythrocytes. In the arterial blood, only from 42 to 75 per cent of the quantity of SH groups demonstrated in the venous blood was found. This indicates a corresponding conversion of the SH forms into disulphide forms in the lungs. An increase of the glutathione content of the blood corpuscles within a few hours was observed in acute anemia, in poisoning with phenylhydrazine and with diminution of the oxygen tension in the inspired air. While the quotient of glutathione and erythrocyte content in normal human blood ranges between 5.3 and 9.3, it increases in secondary anemia to 9.8 and in pernicious anemia to 15.5.

AUTHOR'S SUMMARY.

THE CHIEF DIFFERENCES IN THE CHEMICAL COMPOSITION OF SKIN VESICAL CONTENT AND INTRAVITALLY REMOVED SKIN TISSUES. ERICH URBACH, Klin. Wchnschr. **8**:2094, 1929.

On the basis of comparative analyses of the blood serum, skin vesical fluid and intravitally removed skin, the author disagrees with Gaenslen, Wohlgemut and others who contend that the chemical analysis of fluid in cantharides blisters may replace those of the tissues themselves.

AUTHOR'S SUMMARY (in part).

CHEMICAL EXAMINATIONS OF TISSUES WITH EXPERIMENTAL ROENTGEN REACTIONS. ERICH URBACH AND HANS SCHNITZLER, Klin. Wchnschr. **8**:2179, 1929.

Experiments on animals demonstrate that severe protein injury accompanies reactions following roentgen treatments, manifested by an increase in the total nitrogen and nonprotein nitrogen, which is dependent in individual cases on the dosage and the interval following the exposure. The increase of the total nitrogen

in the blood is about 10 per cent, and in the skin about from 20 to 30 per cent, while the nonprotein nitrogen of the blood and of the skin is increased as much as 300 per cent. Of these, the uric acid nitrogen is markedly increased. That the reaction is a general tissue damage is indicated by the similarity in kind and degree of alterations in the directly irradiated abdominal skin as well as in the protected skin of the back. There is an inverse ratio between the nitrogen and the chloride values in the skin and in the blood. Variations in calcium, potassium, sugar, cholesterol, etc., are explained by the severe general damage to the organism.

EDWIN F. HIRSCH.

Microbiology and Parasitology

VEGETATIVE ENDOCARDITIS DUE TO BRUCELLA MELITENSIS. CLARENCE E. DE LA CHAPELLE, Am. Heart J. **4**:732, 1929.

A case of undulant (Malta) fever due to *Brucella melitensis* is reported which was associated with a vegetative and ulcerative endocarditis of the aortic valves, and which clinically presented the manifestations of subacute bacterial endocarditis. The diagnosis was verified by bacteriologic cultures.

PEARL ZEEK.

CONGENITAL SYPHILIS OF THE THYROID GLAND. WILLIAM C. MENNINGER, Am. J. Syph. **13**:164, 1929.

Three cases of congenital syphilis showing lesions in the thyroid gland and one clinical report of hypothyroidism in a congenital syphilitic girl are reported. Both hypothyroidism and hyperthyroidism occur with congenital syphilis and in some cases unquestionably are a part of the syphilitic process. Hypothyroidism is more frequent and probably results in most cases from the effect of an intrauterine toxin, becoming manifest at an early age. Hyperthyroidism is more probably the result of a localization of infectious process in the gland, and usually does not become evident before adolescence. The thyroid may be increased several times in size, may be of normal size and even smaller. It is usually more firm, and several authentic cases of gumma formation have been reported. Microscopically, the gland usually shows a perivascular connective tissue growth of varying degrees, compressinge the follicles. The latter are often disturbed in their arrangement with the formation of abnormal colloid and with some increase in vascularity. Spirochetes are sometimes absent and sometimes present in great numbers.

AUTHOR'S SUMMARY.

COEXISTENT SYPHILIS AND TUBERCULOSIS. A. L. GALLANT, Am. Rev. Tuberc. **19**:573, 1929.

The coexistence of syphilis and tuberculosis, based on the Wassermann reaction, occurred in 21 per cent of the patients treated; in the Kahn test the incidence was 15 per cent. Syphilis coincident with tuberculosis shows a decidedly unfavorable influence on the tuberculosis in direct proportion to the extent and activity. Markedly beneficial effects were obtained by treatment for syphilis, especially when the activity of the tuberculosis was class B or less. The dosage of the arsenicals should be reduced to one-half or one-third the usual amount.

H. J. CORPER.

REACTIONS OF THE SUBCUTANEOUS CONNECTIVE TISSUE TO EXPERIMENTAL TUBERCULOSIS IN THE GUINEA PIG. M. L. LINDSEY, Am. Rev. Tuberc. **19**:615, 1929.

As the result of an extensive study in guinea-pigs, it is concluded that the fibroblasts may be considered as an interchangeable source of cells which are involved in maintaining an equilibrium of body cells. They seem to be relatively

undifferentiated cells closely related to primitive mesenchyme. The presence and degree of stimulation of these cells are evidenced by changes in type as the result of this stimulation. Fibroblasts are seen to be transformed into exudate cells, including clasmatocytes, monocytes, lymphocytes (small histocytes?), polyblasts, epithelioid cells and, as previously shown, plasma cells and mast cells. A new theory of giant cell formation is suggested from the evidence found in this study. There is no evidence for the formation of polymorphonuclear leukocytes from fibroblasts; pyknotic polyblasts may become lobulated and look like pyknotic polymorphonuclear leukocytes the granules of which have disappeared. Monocytes may originate locally from fibroblasts and represent intermediate stages in epithelioid cell formation.

H. J. CORPER.

UNDULANT FEVER. A. V. HARDY, J. A. M. A. **93**:891, 1929.

The characteristics of *Brucella melitensis* organisms have only recently been fully described. A classification of strains isolated from human beings cannot now be regarded as a reliable index of the importance of different varieties as a cause of human disease. A special effort should be made to obtain a detailed postmortem study in all fatal cases of undulant fever. The pathologic lesions and clinical signs of *Brucella melitensis* infections in animals show a definite correlation. The epidemiologic data, based on the reports of more than a thousand recent cases of undulant fever in the United States, indicate that cattle and hogs with contagious abortion are the sources of these infections. Macroscopic agglutination tests on patients with febrile illness of undetermined etiology should be made more frequently. Additional study is essential in order to determine effective and applicable methods of control.

AUTHOR'S SUMMARY.

ETIOLOGY OF OROYA FEVER: XVI. VERRUGA IN THE DOG AND THE DONKEY. H. NOGUCHI, H. R. MULLER, E. B. TILDEN and J. R. TYLER, J. Exper. Med. **50**:455, 1929.

In the experiments here reported, definite verruca lesions, in which the presence of *Bartonella bacilliformis* was established by culture or by passage to *Macacus rhesus* monkeys, were produced in a dog and in a donkey by inoculation of cultures or of monkey passage strains. The reaction induced in these animals was entirely local, however; blood cultures were sterile. Histologically, the lesions produced were similar to those obtained in monkeys by inoculation of *Bortonella bacilliformis*, except for the presence of a marked polymorphonuclear leukocytic exudate. In another donkey a lesion histologically suggestive of verruca was produced, while in one donkey and a horse the results of inoculation were negative or indefinite. The intravenous injection of a filtrate or of heat-killed cultures of *Bartonella bacilliformis* into two donkeys was followed by the appearance of large, soft, subcutaneous swellings on various parts of the body, not resembling in any way verruca lesions.

AUTHORS' SUMMARY.

DIFFERENTIATION OF HEMOLYTIC STREPTOCOCCI OF HUMAN AND OF DAIRY ORIGIN BY METHYLENE BLUE TOLERANCE AND FINAL ACIDITY. ROY C. AVERY, J. Exper. Med. **50**:463, 1929.

A grouping of 138 strains of hemolytic streptococci based on differences in dye-sensitiveness and in final hydrogen ion concentration of cultures is presented. Three groups are distinguished; human parasitic strains, defined by a final p_H range of 5.2 to 5 and by failure to reduce methylene blue (1:5,000) in milk; bovine strains parasitic in the udder, characterized by a final p_H range of 4.5 to 4.2 and by failure to reduce methylene blue (1:5,000) in milk; saprophytic strains, characterized by a final p_H range of 4.5 to 4.2 and by ability to reduce methylene blue. Methylene blue was bactericidal for the strains of hemolytic streptococci that fail to reduce it, but neither bacteriostatic nor bactericidal for the strains that caused its reduction.

AUTHOR'S SUMMARY.

TOXIC SUBSTANCES OF BACILLUS TYPHOSUS. GREGORY SHWARTZMAN, J. Exper. Med. **50**:513, 1929.

It has been demonstrated that many multiples of minimal doses of *Bacillus typhosus* reacting factors can be neutralized by specific immune serums. The potency of a given serum can be conveniently titrated against increasing amounts of reacting factors. If the immune serum is diluted or if the amount of the reacting factors is too large for a given amount of serum, neutralization is obtained but only irregularly. Normal and heterologous serums (therapeutic meningococcus and erysipelas horse serums) free from normal agglutinins or possessing normal agglutinins of a low titer (1:16) for *B. typhosus* are not able to neutralize the reacting factors. There is obtained questionable neutralization with a serum possessing normal *B. typhosus* agglutinins in dilution 1:64. The titer of the neutralizing antibodies increases in the course of immunization. Immune serums exercise a definite protection against the mortality induced by the intravenous injection of *B. typhosus* culture filtrates.

AUTHOR'S SUMMARY.

INFECTIVITY OF BLOOD DURING THE COURSE OF EXPERIMENTAL YELLOW FEVER. N. PAUL HUDSON and CORNELIUS B. PHILIP, J. Exper. Med. **50**: 583, 1929.

In five *Macacus rhesus* fatally infected with yellow fever virus, the disease ran varied and typical courses, death occurring from eighty-two hours to ten days after infection. Batches of *Aldes aegypti* were fed daily on each monkey, and specimens of blood injected into other animals. By mosquito transfer, the virus was found to be circulating in the peripheral blood one or two days after the infecting and the same interval before the onset of fever; in one instance, mosquitoes became infectious by feeding on a monkey twelve hours after its inoculation. Mosquitoes continued to acquired infectivity during the febrile period and for one day thereafter, except in one instance in which death occurred during fever which prevented postfebrile testing. By subinoculation of blood, the disease was transferred before and after, as well as during the same interval as in mosquito transmission. In one of two attempts, the virus was carried by this means as early as twelve hours after the donor animal was infected. Following the first day of the postfebrile period, blood transmissions were irregularly fatal beyond the period infective for mosquitoes. These results point to a remarkably rapid multiplication of the virus in the animal host, in one case a blood subinoculation (0.5 cc.) being successful at the first test twenty-four hours after the donor monkey was bitten by only two *A. aegypti*. The regular acquisition of infectivity by mosquitoes fed during the incubation period is of especial interest in indicating the infectivity of human cases for mosquitoes before the appearance of clinical symptoms. This offers one explanation for the insidious propagation of epidemics of yellow fever and should be useful in the institution of control activities during an outbreak of this disease.

AUTHORS' SUMMARY.

NASOPHARYNGEAL FLORA IN HEALTH AND DURING RESPIRATORY DISEASE IN ISOLATED COMMUNITIES IN ALABAMA AND LABRADOR. E. L. BURKY and W. G. SMILLIE, J. Exper. Med. **50**:643, 1929.

Studies of the bacterial flora of the nasopharynx were made in isolated communities in southern Alabama and Labrador. The basic flora was determined in both communities. In Alabama, an epidemic of common colds was studied. In Labrador, cases of sporadic colds and an epidemic of tracheitis were studied. Gram-negative cocci were found in nearly all normal persons in moderate numbers. In pathologic states, there was a suppression of these organisms. Staphylococci were found in small numbers in about half of the normal persons. In pathologic conditions, they disappeared from most of those affected but were found in increased numbers in a few persons. Pfeiffer bacilli were absent or present only in small numbers in

normal persons. During the epidemic of colds in Alabama, there was an increase in the number of strains recovered and an increase in the relative numbers of the bacilli in each throat. The highest prevalence was found one month after the epidemic had reached its height. In Labrador, a similar increase was coincident with an epidemic of tracheitis. During normal periods, the majority of the Pfeiffer strains were of the para nonindol-forming type. During epidemic periods, the strains recovered were largely true indol-forming *B. pfeifferi*. Hemolytic streptococci were rarely found in normal persons. During disease prevalence periods, they appeared in a small number of persons. In Alabama, indifferent streptococci resembled the hemolytic streptococci in their distribution. In Labrador, they were found to be widely distributed in both health and disease and composed apparently a part of the normal flora. Green streptococci were found to be widely distributed in fairly large numbers in healthy as well as in sick people. Intermediates, or organisms midway between green streptococci and pneumococci, were found in moderate numbers in each series of persons studied. Early in the Alabama epidemic, they were present in large numbers in nearly all persons. Pneumococci were not found in Alabama in normal persons. The epidemic of colds in Alabama was accompanied by a marked increase in the incidence of these organisms. In Labrador, pneumococci seemed to be part of the normal flora as they were generally distributed throughout the community, in many instances comprising a large proportion of the flora of an individual's throat. The Labrador strains of pneumococci were avirulent. A variety of other organisms such as diphtheroids, gram-negative rods and gram-positive cocci were found in small numbers in many persons both in health and disease.

AUTHORS' SUMMARY.

INFECTION OF MAN WITH BRUCELLA ABORTUS. F. WEIGMANN, Arch. f. Hyg. **102**:77, 1929.

Of thirty-eight patients with undulant fever, seventeen gave a history of contact with cows that had aborted and twelve stated that they drank raw milk. In most of the cases there was a parallelism between the results of serologic examination and the clinical symptoms. The author demonstrated that undulant fever developed in guinea-pigs not only following the peroral administration of milk from infected cows but also following its introduction through the scarified skin by means of inunction. He believes, however, that in man the great majority of cases of undulant fever are caused by drinking infected milk.

IS THE BACTERIUM GRANULOSIS OF NOGUCHI THE CAUSE OF TRACHOMA? K. LINDNER, Arch. f. Ophth. **122**:391, 1929.

Dr. Lindner came to America in the summer of 1928 and examined Noguchi's monkeys at the Rockefeller Institute as well as many of the pupils at the school for American Indians in Albuquerque who are suffering from trachoma, including those from whom Noguchi had obtained his material for bacteriologic study.

After seeing the eyes of the monkeys Lindner came to the conclusion that these experimentally produced conditions have nothing in common with trachoma. He considers trachoma to be an inflammation of the conjunctiva of long duration which in every case leads to a thickening at least of the conjunctiva. But in Noguchi's monkeys "the conjunctiva itself was normal in every case, delicate throughout and transparent, even after the disease had lasted a long time and there had been an increase in the number of follicles. The lymphatic tissue of the conjunctiva alone was simultaneously diseased." He "found no trace of cicatrization in any of the animals demonstrated to me, aside from scars resulting from excision of the conjunctiva. . . . The conjunctival disease produced by Noguchi differs from that which we know of the beginning and course of experimental trachoma. In none of Noguchi's animals were there an immediate, general inflammation of the conjunctiva with purulent secretion, such as has been noted

by many observers. . . . Inoculation with *B. granulosis* on the other hand, leads at first to a local inflammation at the site of inoculation. There the first granulations appear; they spread over the conjunctiva only as a secondary manifestation.

". . . The Noguchi bacillus is found only in the subepithelial tissue, not at the conjunctival surface, whereas the trachoma virus can always be found in the secretion also. . . . Noguchi remarks that the follicles formed lie as if in capsules, that is, sharply delimited; this in an animal 37 days after infection. In trachoma such an encapsulation at the beginning of the disease is never observed. It corresponds, moreover, to the clinical picture of folliculosis."

From the impression the author received of the condition in the eyes of the monkeys, he expected to find no true trachoma among the school children whom Noguchi had studied in Albuquerque. On the contrary, a large proportion of the children examined showed a typical trachoma, and the inclusion bodies of von Prowazek could be demonstrated. Of the three persons of the four from whom Noguchi obtained the material for inoculation, one was without signs of trachoma, but two were definitely trachomatous, in the third stage.

The author points out the fact that many experimenters have found *Macacus rhesus* to be highly resistant to inoculations with material from trachomatous eyes; the orang-utang more suitable. But Noguchi had little success with orang-utangs. The author concludes that Noguchi has not isolated the cause of trachoma, but has probably found the agent, or one of the agents, of folliculosis.

CHARLES WEISS.

EXPERIMENTAL INVESTIGATION OF POSTVACCINAL ENCEPHALITIS. E. BERGER, Centralbl. f. Bakteriol. **110**:138, 1929.

Berger attempts to test in rabbits certain ideas as to the relationship between vaccination and postvaccinal encephalitis, but all of his experiments yielded negative results and failed to substantiate any of the theories tested.

PAUL R. CANNON.

THE SPIROCHETE CONTENT OF THE CORNEA AFTER SUBSCROTAL SYPHILIS INOCULATION. SHIGERU INO, Klin. Wchnschr. **8**:2193, 1929.

The cornea, like the lymph nodes in rabbits with scrotal infection, is a spirochetes reservoir, even when inflammatory reactions are absent. Arsphenamine in the usual doses kills the spirochetes.

AUTHOR'S SUMMARY.

Immunology

THE PRODUCTION OF ALLERGIC INFLAMMATION IN THE KIDNEYS. OPAL E. HEPLER and J. P. SIMONDS, Am. J. Path. **5**:473, 1929.

Hemorrhage was found in the kidneys of every animal into which injections had been made, if the animal was killed within seventy-two hours. Necrosis was observed in kidneys of sensitized rabbits only. Anaphylactic inflammation differs from other inflammation in the intensity and rapidity with which it occurs. This anaphylactic inflammation was caused by the direct toxic effect of the antigen on the sensitized tissues.

AUTHORS' CONCLUSIONS.

CHEMO-IMMUNOLOGICAL STUDIES ON CONJUGATED CARBOHYDRATE-PROTEINS. W. F. GOEBEL and O. T. AVERY, J. Exper. Med. **50**:521, 533, 1929.

The synthesis of *p*-aminophenol β-glucoside and *p*-aminophenol β-galactoside has been described. These hexosides have been coupled to serum globulin. Two protein sugar complexes with different optical properties have been obtained.

When two chemically different carbohydrate derivatives are bound to the same protein, the newly formed antigens exhibit distinct immunologic specificity. When the same carbohydrate radical is conjugated with two chemically different and serologically distinct proteins, both of the sugar-proteins thus formed acquire a common serologic specificity. The newly acquired specificity of the artificially prepared sugar-proteins is determined by the chemical constitution of the carbohydrate radical attached to the protein molecules. Simple differences in the molecular configuration of the two isomers—dextrose and galactose—suffice to orientate protein specificity when the corresponding glucosides of the two sugars are coupled to the same protein. The unconjugated glucosides, although themselves not precipitable in immune serum, inhibit the reaction between the homologous sugar-protein and its specific antibody. The inhibition test is specific. The sugar derivatives unattached to protein exhibit the properties of carbohydrate haptins; they are nonantigenic but specifically reactive, as shown by inhibition tests, with antibodies induced by proteins containing the homologous diazotized glucoside. The specificity of artificially prepared sugar-proteins is discussed with reference to the chemo-immunologic nature of the bacterial antigens containing complex sugars.

AUTHORS' SUMMARY.

ACTIVE AND PASSIVE ANAPHYLAXIS WITH SYNTHETIC SUGAR-PROTEINS. W. S. TILLETT, O. T. AVERY and W. F. GOEBEL, J. Exper. Med. **50**:551, 1929.

Guinea-pigs passively sensitized with the serum of rabbits immunized with an artificially prepared sugar-protein (glucoglobulin) exhibit typical anaphylactic shock when subsequently inoculated with gluco-albumin; the serum of rabbits immunized with a second synthetic sugar-protein (galactoglobulin) similarly sensitizes guinea-pigs to galacto-albumin. The reactions in each instance are specific and depend for their specificity on the carbohydrate component, and not on the protein fraction of the synthesized sugar-protein. Guinea-pigs actively sensitized with gluco-globulin or galacto-globulin are similarly subject to anaphylactic shock when, after twenty-one days, they are given injections of sugar-proteins containing carbohydrate identical with that present in the sensitizing antigen, regardless of the kind of protein with which it is combined. The unconjugated glucosides, although themselves not capable of inducing shock, inhibit the anaphylactic reaction when injected immediately prior to the introduction of the toxigenic sugar-protein. The protective action of the glucosides disappears within two hours after injection. In order to elicit the phenomenon, the carbohydrate must be the same as that combined in the sugar-protein complex. Anaphylactic shock may be induced by uncombined globulin in guinea-pigs passively sensitized with either antigluco-globulin serum or antigalacto-globulin serum; globulin is similarly effective in animals actively sensitized with glucoglobulin or galactoglobulin. The reactions elicited by globulin alone are dependent on the common protein present in the antigens, and exhibit only species specificity.

AUTHORS' SUMMARY.

ACTIVE IMMUNIZATION OF MICE AGAINST TYPE II PNEUMOCOCCI BY VACCINATION WITH YEAST. J. Y. SUGG, L. V. RICHARDSON and J. M. NEILL, J. Exper. Med. **50**:579, 1929.

Mice vaccinated with yeast were protected against subsequent infection with type II pneumococci, but not against types I or III. While the protection was not universal, as high a percentage of mice acquired active anti-type II immunity, as was obtained by vaccination of another group of mice with type II pneumococci. This specific protection of mice by active immunization with the yeast antigen, is probably due to the same immunologic relationship responsible for the anti-type II reactivity of the antiserums of rabbits immunized with yeast antigen.

AUTHORS' SUMMARY.

A Study of Vaccinal Immunity in Tissue Cultures. T. M. Rivers, E. Haagen and R. S. Muckenfuss, J. Exper. Med. **50**:673, 1929.

Normal corneas inoculated in vitro with vaccine virus and then cultivated in antivaccinal plasma developed typical vaccinal lesions associated with Guarnieri's bodies. In such cultures, after an incubation period of twenty-four or forty-eight hours, active vaccine virus was demonstrated by means of appropriate methods. Immune corneas inoculated in vitro with vaccine virus and then cultivated in normal or in antivaccinal plasma revealed either mild vaccinal lesions or none at all. In some of the cultures after twenty-four and forty-eight hours of incubation, active vaccine virus was demonstrated.

Authors' Summary.

Cutaneous Reactions to the Polysaccharides and Proteins of Pneumococcus in Lobar Pneumonia. W. S. Tillett and T. Francis, Jr., J. Exper. Med. **50**:687, 1929.

Pneumococcus polysaccharides, when injected intradermally into patients convalescent from pneumonia, are capable of eliciting a response. The polysaccharide inducing a cutaneous reaction was found always to be homologous in type to that of the pneumococcus causing the infection. The character of the reaction incited by the protein-free bacterial sugars is of the immediate wheal and erythema type. A patient's capacity to react was found to be intimately associated both with recovery from infection and with the presence of type specific antibodies in the circulating blood. The so-called nucleoprotein of pneumococcus, when injected intradermally, also causes a local cutaneous reaction in patients during convalescence from lobar pneumonia. The local lesion resulting from the injection of protein is tuberculin-like and differs from that evoked by the type-specific polysaccharides in gross appearance, time of development and duration. Persons who are acutely ill with and convalescent from pneumococcus pneumonia possess in their circulating blood precipitins that are reactive with pneumococcus protein. In the observations recorded, the concentration of antiprotein antibodies in the blood serum did not seem to influence the patient's capacity to react to intradermal injection of the protein.

Authors' Summary.

A Precipitin Test in Experimental Trichiniasis. George W. Bachman, J. Prev. Med. **3**:465, 1929.

The present work corroborates the previous conclusions that precipitins can be demonstrated in the serums of rabbits infected with *Trichinella spiralis* from twenty to thirty days after infection, when one uses an antigen prepared from isolated larvae dried, ground and extracted with 0.01 normal hydrochloric acid in 0.85 per cent sodium chloride. A comparative study of the results with this acid antigen and with another antigen prepared with Coca's solution (768 precipitation tests on twenty rabbits) showed that the latter was the more potent, precipitin antibodies being detected in from five to twenty days after infection. When using the antigen prepared with Coca's solution, it is thus possible to detect the infection during the period of ingression; that is, while the adult worms are still in the small intestine and before the larvae have entered the blood stream.

Author's Summary.

Complement Fixation in Experimental Trichiniasis. George W. Bachman and Paris E. Menendez, J. Prev. Med. **3**:471, 1929.

The titers of eight *Trichinella* infested rabbits, on which 150 complement-fixation tests were run, rose on the third day after infection and then dropped from the fifteenth to twentieth day after infection. From the twenty-fifth day to the thirty-fifth (the end of the experiment) the titer increased very rapidly. Due to the great variability in the titer and the nonspecific reaction of the serum

of rabbits, it is questionable whether the test is practicable until the twenty-fifth day of infection, at which time the antibody formation is of such a concentration as to over-rule the nonspecific action of the serum.

AUTHORS' SUMMARY.

THE SEROLOGICAL RELATIONSHIPS OF TWENTY-SIX STRAINS OF PASTEURELLA. J. T. CORNELIUS, J. Path. & Bact. **32**:355, 1929.

It has been possible by means of agglutinin-absorption tests to group seventeen *Pasteurella* strains out of twenty-six; group I containing seven, group II five, group III three and group IV two strains; the remaining nine strains defied classification. Complement-fixation tests carried out with two group I strains and a number of serums partially confirmed this grouping. No relationship between the serologic group and the animal origin of the strains was evident.

AUTHOR'S SUMMARY.

THE PASSAGE OF ANTIBODIES INTO THE AQUEOUS HUMOUR AND ITS RELATION TO THE FORM OF THE SOLUTION. A. FRANCESCHETTI and C. HALLAUER, Arch. f. Augenh. **100-101**:81, 1929.

Although the permeability of the aqueous humor for antibodies is increased by the effect of diuretics, the passage of substances into the media of the eye is controlled not only by the condition of the "filter" (the aqueous humor barrier) but also by the physicochemical condition of the permeating substance. The authors have tested this fact, using plasma, serum and serum albumin fractions.

In rabbits, the antibody (agglutinin) passes into the aqueous humor more easily when it is in the form of a serum globulin than in the form of native, unaltered serum injected intravenously. There is no difference in the transfer of antibody-containing euglobin and antibody-containing pseudoglobulin (from the same homologous immune serum) as regards the ease with which the passage is made.

CHARLES WEISS.

IMMUNIZATION AGAINST TUBERCULOSIS BY MEANS OF B.C.G. BELONOWSKI, Centralbl. f. Bakteriol. **110**:184, 1929.

Belonowski, in tissue cultures of human lymphocytes, tested their reaction to virulent tubercle bacilli and to B.C.G. A colored plate illustrates his observations, namely, that with virulent tubercle bacilli there is quickly a marked necrosis of the cells with death of the culture. At times the development of tubercles, with caseous necrosis, giant cells, etc., is observed, but usually the cultures die rapidly. With B.C.G., however, the cells develop well and the majority of the lymphocytes become epithelioid cells; these remain intact and show a vigorous phagocytosis, the phagocytosed microbes losing their shape and apparently being digested. Furthermore, cultures of lymphocytes after having been in contact with B.C.G. for twenty-four hours seem to acquire some immunity to virulent tubercle bacilli in that they are not so quickly injured by the latter as they are without this previous treatment.

PAUL R. CANNON.

THE RETICULO-ENDOTHELIAL SYSTEM AND IMMUNITY. BIELING, Centralbl. f. Bakteriol. **110**:195, 1929.

This paper, with seven colored figures, consists of a general discussion of the distribution and significance of the reticulo-endothelial system with reference to its rôle in resistance to infectious disease. The newer experimental investigations are summarized and discussed, particularly the problem of blockade. The author concludes that immunity should be considered as a property of the entire organism and that the old strife as to the relative importance of humoral and cellular elements is of no great importance as the immune process depends on both.

PAUL R. CANNON.

SYPHILIS IMMUNITY AND SYMPTOMLESS SYPHILITIC SUPERINFECTION. R. PRIGGE and E. V. RUTKOWSKI, Deutsche med. Wchnschr. **55**:1508, 1929.

Material from a left inguinal lymph node removed from an untreated patient with paresis did not produce syphilis when injected into rabbits. The right thigh of this patient was scarified and inoculated with material from a syphilitic lesion of a rabbit containing spirochetes with considerable virulence for rabbits. No symptoms resulted from this and the skin healed rapidly. Ninety-three days later four mice were inoculated with material from a lymph node removed from the right groin. The mice were killed after being perfectly well for a year, and material from the axillary and inguinal lymph nodes and the brain was inoculated into the scrotum and testes of four rabbits. Three of the four rabbits developed lesions in which spirochetes were demonstrated. The authors conclude that immunity in syphilis may be only a false immunity which, while it inhibits chancre formation in a reinfection, does not protect against the penetration of virulent spirochetes into the lymph nodes and other tissues of the body.

PAUL J. BRESLICH.

PROTECTIVE INOCULATION OF CATTLE AGAINST BOVINE TUBERCULOSIS WITH SLIGHTLY VIRULENT BOVINE TUBERCLE BACILLI. UHLENHUTH, A. MÜLLER and K. HILLENBRANDT, Deutsche med. Wchnschr. **55**:1535, 1929.

Cattle from 4 to 6 months old with negative tuberculin reactions were divided into four groups of six each. The first group was inoculated subcutaneously with 100 mg. of B.C.G. and the second group with 100 mg. of an old culture of bovine tubercle bacilli grown on artificial mediums since 1902. This culture inoculated into guinea-pigs produced a form of tuberculosis which usually healed in nine months. The third group of cattle received 1 Gm. of the avirulent culture intraperitoneally, while the fourth group received none. After from one to three months all the animals were placed with cattle known to have tuberculosis of the lungs and with tubercle bacilli in the sputum. At postmortem examination of these four groups of cattle, it was found that two in each of the first three groups had no tuberculosis, while all of the uninoculated control animals were infected. The authors think it highly improbable that the inoculations produced any effective immunity against tuberculosis in these cattle.

PAUL J. BRESLICH.

SPONTANEOUSLY HEALED DIPHTHERIA. FRANZ HAMBURGER and J. SIEGL, München. med. Wchnschr. **76**:1537, 1929.

Among twenty patients whose mild forms of diphtheria had been allowed to heal without injections of antitoxin, fifteen gave positive Schick reactions a short time after convalescence. These results indicate that free antitoxin is not demonstrable in a large number of patients with spontaneously healed diphtheria.

EDWIN F. HIRSCH.

IMMUNIZATION OF MAN WITH HUMAN BLOOD. O. THOMSEN, Ugesk. f. laeger **91**:776, 1929.

The results tend to indicate that blood of one type has no antigenic power in persons of other types and that it is rather doubtful whether the differentiation into type rests on an antigenic basis.

Tumors

TUBERCULOSIS AND MALIGNANT TUMOR. LEO V. SCHNEIDER, Am. Rev. Tuberc. **20**:271, 1929.

Active, progressive tuberculosis associated with any form of malignant tumor is rather uncommon. It is difficult to demonstrate tubercle bacilli in the sputum of patients suffering from both tuberculosis and malignant growth. Sputum should

be examined repeatedly. The coexistence of pulmonary tuberculosis and malignant tumor is extremely rare before the age of 35.

H. J. CORPER.

OSTEITIS FIBROSA AND GIANT CELL TUMOR. C. F. GESCHICKTER, M. M. COPELAND and J. C. BLOODGOOD, Arch. Surg. **19**:169, 1929.

There is a foreword by Dr. Bloodgood. This is an extensive article covering lesions of bones ranging from bone cysts to giant cell tumors and epulis and xanthomas of the tendons. Over 400 lesions were studied, and from their studies the authors conclude that osteitis fibrosa, osteitis cystica, bone cysts of various types, giant cell tumors, xanthoma tumors and epulis all bear a genetic relationship to each other. They feel that the cystic lesions result from healing processes occurring in the giant cell tumor, and were able to demonstrate several transitional lesions. The part played by the osteoclasts is stressed, in that they feel that they can demonstrate that these cells play a rôle in the transition process, changing the bone by canalizing it and stimulating blood vessel formation. This transition occurs chiefly in calcified cartilage, as seen in the epiphyseal regions and in the cartilaginous centers of the flat bones. The same applies to epulis, where there are temporary calcified structures at the roots of the teeth, and in xanthomas of the tendon sheaths they find that these occur in association with the sesamoid bones. They view all these lesions as neoplasms, and stress the importance of trauma in their etiology, maintaining, however, that there is a primary cellular proliferation not inflammatory in origin.

N. ENZER.

THE INFLUENCE OF DILUTION ON THE CARCINOGENIC EFFECT OF TAR. I. HIEGER, J. Path. & Bact. **32**:419, 1929.

A carcinogenic agent (ether extract of tar) was tested on mice in three concentrations, namely in the undiluted state (100 per cent concentration) and in 10 and 1 per cent dilutions of this. The reduction in strength from 100 to 10 per cent delayed the earliest appearance, but did not lessen the total yield of tumors or the average induction period. On the other hand, the diminution from 10 to 1 per cent, while prolonging the induction period, has reduced the production of tumors to an extremely low total. Hence the experiment shows that an increase in concentration of the carcinogenic agent beyond a certain point does not increase the number of tumors.

AUTHOR'S SUMMARY.

THE MODIFYING INFLUENCE OF DICHLOROETHYL SULPHIDE ON THE INDUCTION OF TUMOURS IN MICE BY TAR. I. BERENBLUM, J. Path. & Bact. **32**:425, 1929.

The addition of 0.1 per cent mustard gas to a carcinogenic tar inhibits the tar from inducing tumors. This anticarcinogenic effect of mustard gas is due to its action on the animal, so that the skin no longer responds to a carcinogenic tar. The induction of warts is still inhibited if the mustard gas is added to the tar as late as the eleventh week of tarring.

AUTHOR'S SUMMARY.

SEROLOGIC SPECIFICITY OF CARCINOMA CELLS. L. HIRSZFELD, W. HALBER and J. LASKOWSKI, Klin. Wchnschr. **8**:1563, 1929.

The results of the experiments recorded indicate that many carcinomas, especially gastric, contain lipoid of special serologic character.

THE SIGNIFICANCE OF ALKALINE REACTION IN THE GROWTH OF CARCINOMA. J. FLASZEN and H. WACHTEL, Klin. Wchnschr. **8**:1912, 1929.

Carcinomatous tissues of the mouse suspended in 0.1 per cent sodium bicarbonate, 0.1 per cent sodium hydroxide or 0.1 per cent ammonia solution and injected into

mice grow faster and lead to the death of the host sooner than similar tissues not suspended in an alkaline medium. Alkalinization of a carcinomatous mouse causes a marked accentuation of the growth. Alkalinization of healthy mice favors markedly the subsequent tumor implantation.

AUTHORS SUMMARY.

ON CARCINOMA OF THE PENIS AND ITS PARTICULAR FREQUENCY IN EAST ASIA. E. A. DORMANNS, Ztschr. f. Krebsforsch. **29**:435, 1929.

The writer has observed five cases of carcinoma of the penis during the routine examination of a few hundred sections, in the course of his one and one-half years at Canton. Discussing the frequency of this cancer not only in China, but as well in Java and the Malay States, he speculates as to its cause, calling attention to the frequency in those regions of skin diseases in general, to increased climatic exposure, and to the possibility of irritative action by remedies of the Chinese pharmacopeia.

H. E. EGGERS.

RESULTS OF THE CYTOLOGIC STUDY OF TUMORS. B. LIPSCHÜTZ, Ztschr. f. Krebsforsch. **29**:440 and 449, 1929.

In these two reports the writer announces the demonstration of intracellular bodies, similar to those previously reported by him in the Rous sarcoma and in the inoculable mouse sarcomas, inoculable mouse carcinoma and rat sarcoma. The carcinoma bodies showed distinguishing criteria corresponding to the biologic differences in this tumor.

H. E. EGGERS.

THE QUESTION OF THE SPONTANEOUS HEALING OF CANCER. R. FRAUCHIGER, Ztschr. f. Krebsforsch. **29**:516, 1929.

In a critical review of reported cases of spontaneous recovery from cancer, including a number of cases carefully investigated by the writer, she finds that from the point of view of extreme criteria — concordant clinical and histologic diagnoses, subsequent history and negative autopsy observations — there has been no known case of spontaneous healing. A number of cases have shown apparent healing for periods as long as four years, but autopsy observations are lacking in these. A similar objection may be made to a number of cases in which there had been insufficient or palliative operative procedures. There are a number of cases of apparently spontaneously healed cancer of the skin. Attention is called to the fact that recurrence or metastasis may be delayed as long as forty years. There are, however, undoubted cases of spontaneous regression.

H. E. EGGERS.

THE GENESIS OF CHORIO-EPITHELIOMA. H. NEVINNY, Zentralbl. f. Gynäk. **53**:908, 1929.

Twelve orthotopic chorio-epitheliomas were studied for the relation of the vessels to the location of the tumor. In three of six especially investigated cases large masses of cells were found surrounding the vessels of the main tumor and partly also those of the metastases. The endothelial lining was always preserved. The perivascular tumor cells may have originated from two sources. They represent either tumor cells which proliferated in the perivascular tissue or they originated from mesenchymatous elements of the vascular wall. As the existence of perivascular lymphatics is not generally recognized, as the regionary lymph nodes were free from tumor cells and as there were no compression symptoms in the perivascular tissue, the author does not accept the possibility of a perivascular proliferation of the tumor in the lymphatics or tissue spaces. He believes rather that the chorio-epithelial cells originate from vascular cell elements of germinative character. The fact that the perivascular proliferation was especially marked in three young women is regarded in favor of his conception.

W. C. HUEPER.

Technical

INTRAVITAL STAINING OF MICROGLIA WITH TRYPAN BLUE. D. S. RUSSELL, Am. J. Path. **5**:451, 1929.

The intravital staining of microglia with trypan blue is demonstrated, using aseptic puncture wounds of the cerebrum as a stimulus to phagocytic activity. It is claimed that such intravital staining identifies microglia with the rest of the reticulo-endothelial system of the body. These conclusions offer further support to Hortega's contention that microglia is a mesodermal element. There is no evidence of the formation of "Gitterzellen" from neuroglia or that neuroglia is able to take a vital stain.

AUTHOR'S SUMMARY.

THE SCHILLING BLOOD DIFFERENTIAL COUNT IN TUBERCULOSIS. J. F. BREDECK, Am. Rev. Tuberc. **20**:52, 1929.

The Schilling blood differential count alone cannot establish the diagnosis of tuberculosis but offers the best single guide in determining the progress of the disease. It is the most delicate index for interpreting the phase and degree of focal activity. Subcutaneous tuberculin can produce all of the characteristic blood changes that one finds in the Schilling blood differential count in active tuberculosis. Changes in the blood differential count after the injection of tuberculin occur before the fever reaction, and with smaller doses of tuberculin than those that induce fever. The Schilling procedure, together with the subcutaneous tuberculin test, constitute the most delicate and most accurate methods in the diagnosis of early manifest and induced focal activity. A shifting of the neutrophilic leukocytes to the left in the Schilling blood differential count is a constant observation in clinically active tuberculosis. The monocytes play an important rôle in the early activity of tuberculosis and in the late healing stages of the disease. An increase of monocytes may be significant as a sign of progression of disease or as a sign of healing. Lymphocytes are also important and show an increase with healing and a diminution with progression of the disease. A high lymphocyte count, with an increase in monocytes and with little or no change in neutrophils, indicates healing. A drop in lymphocytes and an increase in monocytes, with an increase in the shifting to the left of the neutrophils indicate active progression of the disease.

H. J. CORPER.

RESORCINOL TESTS IN RELATION TO DISEASES WITHOUT CONCOMITANT TUBERCULOSIS. ADELAIDE B. BAYLIS, Am. Rev. Tuberc. **20**:79, 1929.

The methods of Vernes and Baylis are in most instances in accord, and while the simplified test lacks the precision and delicacy of interpretation it may be used with satisfactory results when, and only when, the apparatus of Vernes is not available. Certain diseases may give false reactions, and caution should be exercised in diseases without concomitant tuberculosis when a diagnostic result appears, this being especially applicable to inflammatory conditions of the respiratory tract. These observations should be supported by clinical evidence and further laboratory examination of a microscopic nature or animal inoculation. While the resorcinol tests are capable of rendering in many instances a differential diagnosis, their chief value lies in their ability to measure the degrees of activity in a recognized tuberculous infection.

H. J. CORPER.

Society Transactions

PHILADELPHIA PATHOLOGICAL SOCIETY

Dec. 12, 1929

J. HAROLD AUSTIN, *Presiding*

VESICOVAGINAL AND RECTOVAGINAL FISTULAS FOLLOWING APPLICATION OF RADIUM FOR RECURRENT CARCINOMA OF THE VAGINAL VAULT, WITH DEATH FROM UREMIA. LEWIS C. SCHEFFEY.

The autopsy specimens were exhibited from a woman, aged 41 at the time of death in 1928. In 1914 she had had a right salpingo-oophorectomy, and in 1921 a vaginal hysterectomy for squamous cell carcinoma of the cervix. Six weeks after hysterectomy, a recurrence was discovered in the vaginal vault, and a local application of 100 mg. of radium was made for twenty-four hours. Soon after this, vesicovaginal and rectovaginal fistulas developed which persisted. Two weeks prior to the final admission she developed pain in the left flank, fever, nausea and vomiting. On admission, the patient had some of the manifestations of intestinal obstruction, but soon a diagnosis of uremia was established. Convulsions developed and death occurred in twenty-four hours.

At autopsy, no metastases or any evidences of carcinoma were found. The right kidney showed hydronephrosis, the right ureter being thickened and obliterated near its entrance to the bladder. The left kidney showed pyonephrosis, accompanied by a greatly thickened but patent ureter exuding pus. The bladder contained fecal material, as the vesicovaginal fistula was in close proximity to the rectovaginal one.

Striking features of this case were the massive destruction of the kidney following infection of the bladder and entire urinary tract after the production of the fistulas; the prolongation of life for nearly seven years in the presence of such infection; the absence of recurrent carcinoma, either gross or microscopic, in the vagina, pelvis or abdomen.

A RAPID METHOD FOR THE PREPARATION OF PARAFFIN SECTIONS. B. L. CRAWFORD.

This method is particularly applicable to examination of small pieces of tissue removed for biopsy, when frozen section method is not applicable. The method may be completed within from six to twenty-four hours as necessary. If desired, serial sections may be cut and many examined from various levels of the tissue, thus affording adequate material for a careful study from which to submit a reliable histologic report.

1. Place small pieces of tissue, not more than 2 mm. thick, for one-half hour or longer in "alcoholic formol" (Lavdowsky: Anat. Hefte **4**:361, 1894):

Alcohol (95 per cent)	20 parts
Formol	6 parts
Acetic acid	1 part
Water	40 parts

2. Dehydrate in acetone, making three changes to pure acetone each time, three fourths of an hour each.

3. Clear in benzene fifteen minutes or longer until tissue is transparent.

4. Infiltrate in fresh paraffin one hour or longer.

5. Block, cut, mount and stain in the usual way.

CULTURE VERSUS GUINEA-PIG INOCULATION FOR IDENTIFICATION OF THE TUBERCLE BACILLUS. C. J. BUCHER.

The methods usually employed in the diagnosis of tuberculosis, are a search for acid-fast bacilli in stained smears and the inoculation of guinea-pigs, in the hope that the disease may be reproduced in the animal.

These methods, while useful, have certain objections. Even with the most careful search, tubercle bacilli are often not found in smears. Inoculated animals often die of infections from extraneous sources or of those carried by contaminants in the inoculated material. Moreover, accidental infection of guinea-pigs with *Bacillus tuberculosis* has been recorded (Sewall), and certain German investigators believe that some strains of human tubercle bacilli are not pathogenic for guinea-pigs.

In an effort to find a more reliable and economical method to supplant guinea-pig inoculation in the identification of the tubercle bacillus, and one which at the same time would be free from intricate technicalities, I have employed the method of Corper and Uyei for the cultivation of the bacillus directly from suspected material.

Seventy-two cultures were made from pathologic material, some known to contain tubercle bacilli and some in which there was no substantial evidence that the organisms were present. This material included sputum, urine, feces, spinal fluid, pleural fluid, pus aspirated from a bronchus, pus from a cold abscess and human tissue. Stained smears of all specimens were examined microscopically. Portions of forty-two of them were inoculated into guinea-pigs. Twenty-two of the seventy-two cultures examined were positive for *Bacillus tuberculosis*. Ten of these represented material, a portion of which had been inoculated into guinea-pigs. Of these, a positive culture was obtained twice with negative results in the animals, and once a negative culture was obtained while the inoculated animal developed tuberculosis. The failure to obtain a positive culture in the last instance was due to the growth of a mold on the culture medium.

The method is as reliable as the older methods; it is simple as far as technical details are concerned; and it is more economical than guinea-pig inoculation.

THE DIFFUSIBILITY OF CALCIUM IN ALLERGIC DISORDERS. A. CANTAROW.

Previously reported investigations of calcium balance in allergic disorders have concerned themselves with the determination of total serum calcium and of calcium intake and output. These studies have, in the great majority of instances, revealed no deviation from the normal and have led to the belief that no demonstrable disturbance of calcium metabolism exists in these conditions. Since the work of Rona and Takahashi, establishing the partition of serum calcium into diffusible and nondiffusible fractions, considerable evidence has accumulated to indicate that the physiologic activity of calcium is dependent on the various forms in which it exists. A disturbance of the ratio between the diffusible and nondiffusible fractions may occur, with distinct physiologic effects, without any alteration in the level of total serum calcium.

The present study consists of the determination of the diffusibility of calcium in twenty-five patients with bronchial asthma; three with mucous colitis, two with vasomotor rhinitis, one with angioneurotic edema and sixty-three with pulmonary tuberculosis. The method employed consists in the determination of the calcium content of blood serum and cerebrospinal fluid withdrawn at the same time in each case. The spinal fluid calcium is termed "diffusible," although "diffused" is probably more correct. The difference between this figure and the total serum calcium is the nondiffusible portion.

The observations appear to indicate that in bronchial asthma and allied disorders there is a definite and constant disturbance of calcium balance in the form of an increase in the ratio of diffusible to nondiffusible calcium. It is conceivable that this observation is related in some way to the increased cellular permeability which is believed to exist in these conditions.

In chronic pulmonary tuberculosis there is considerable variation in the diffusibility of calcium. It seems that an increased diffusibility ratio is associated with an exudative type of lesion with a high degree of clinical activity, while a decreased diffusibility ratio is associated with a productive process, relatively benign clinically. Whether or not these observations bear any relation to the problem of allergy in tuberculosis cannot be stated definitely.

THE EXPERIMENTAL PRODUCTION OF CHRONIC FOCI OF INFECTION. V. H. MOON.

The methods commonly used for infecting animals in order to determine the pathogenicity of bacteria are inadequate in many instances. Frequently the inoculated animals either succumb or recover promptly, and the procedure does not approximate the conditions present in disease in man. A new method for producing chronic foci of infection has been developed in the Department of Pathology of Jefferson Medical College.

Applicators of cotton, similar to those commonly used for throat swabs, are made on no. 20 or no. 22 rustless wire rather than on wood. The cotton is wound rather loosely so that moderate force will slip it off the wire. A trocar and cannula are inserted into the region to be inoculated. The trocar is then withdrawn leaving the cannula in place. The cotton applicator is dipped into the material to be inoculated and is inserted through the cannula. The swab is pushed beyond the end of the cannula; then, on withdrawing the wire, the end of the cannula pushes off the cotton into the tissue or cavity desired to be infected. The cannula is then withdrawn.

The method is merely a simplified procedure for implanting infection in a porous foreign substance within the tissues. The foreign substance serves to maintain the infection against effective body resistance. The method is well suited for producing chronic foci in subcutaneous and intramuscular areas and in the body cavities. By exposing the abdominal viscera the infection may be implanted easily in the spleen, liver, gallbladder or other structures. In such instances, a smaller cannula and correspondingly smaller applicators are used. For small animals a spinal puncture needle of large size makes a suitable cannula. The cotton swab, on fine stiff wire, is wound small enough to pass readily through the lumen of the needle.

Dogs are so resistant to ordinary inoculations that they are seldom used for the purpose. They are well adapted to this method. When inoculated with streptococci, masses of inflammatory granulations, from 3 to 5 cm. in diameter, develop in a few weeks. The organism is regularly recovered from the area inoculated and frequently from the blood and from the substance of other organs. Hemolytic streptococci and *S. viridans* are recovered in pure culture after six months' implantation.

The organic changes produced in young dogs and rabbits include acute nephritis, endocarditis, arthritis, infarcts, splenic atrophy and fibrosis, periportal inflammation in the liver, lymphadenitis, etc. Detailed results will be given later.

Regular Meeting, Jan. 9, 1930

J. HAROLD AUSTIN, *President*

THE EFFECT OF HIGH FREQUENCY SOUND WAVES ON CELLS AND TISSUES. E. NEWTON HARVEY, Professor of Physiology, Princeton University.

When a quartz crystal, cut in a certain plane, is compressed, it becomes charged positively on one side and negatively on the other, the piezo-electric effect. Conversely, if a quartz crystal is charged positive on one side and negative on the other, it will compress. Reversing the charges causes expansion. If the reversing

of the charges is carried out rapidly by an oscillating electric field, sound waves of a frequency corresponding to the frequency of the oscillating field will be produced, which travel through a medium in contact with the crystal. Wood and Loomis (*Philosophical Magazine* **4**:417, 1927) have described a high power (2 kilowatt) oscillator and Harvey and Loomis (*Nature* **121**:622, 1928) a low power (75 watt) oscillator and crystal for use on the microscope. Frequencies of 300 to 2,500 kilocycles have been employed by the author in collaboration with Mr. A. L. Loomis to study effects on living cells. The sound waves cannot be heard, but have definite mechanical effects. A drop of water is broken into a fine mist. Elodea cells show rapid whirling of the chloroplasts and breaking up of these bodies and the plasma membrane. Blood corpuscles are laked, provided they are not thrown into nodes of standing waves. Egg cells and infusoria are cytolized, and the more easily the larger the cells. Bacteria can be broken up by high intensity sound waves and the suspension sterilized, but complete destruction takes a long time. Skeletal muscle, nerve and luminous cells are not readily stimulated. Quiescent isolated turtle and frog ventricle can be made to beat with regular rhythm. Beating auricles will beat more rapidly. Small fish can be killed, and the cause of death appears to be hemolysis and rupture of gill membranes. From the stirring of cell contents, conclusions can sometimes be drawn regarding the viscosity of cells. No difference in effect can be detected with different frequencies. None of the effects mentioned are due to heating of the cells or to electric influences in the high frequency field. The cytolysis of cells has been shown by Johnson (*J. Physiol.* **67**:356, 1929) to result from the cavitation or removal of dissolved gases from solution. In gas free solutions or solutions under pressure, cells are unharmed.

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Dec. 23, 1929

HARRISON S. MARTLAND, President

ADENOFIBROSARCOMA OF THE BREAST. LAWRENCE SOPHIAN (by invitation).

This is a survey of sarcomas of the breast, undertaken with the object of differentiating the group that may be traced through a stage in which epithelial elements are present. The stimulus for this study arose in the accidental finding of a case of tumor of the breast in which the histologic observations were similar to those in the ordinary adenofibroma with the exception that the fibroblastic tissue was actively growing in the form of a fibrosarcoma. Attempts to find authority for giving the prognosis in such a case made it apparent that no data were available. Subsequently a similar case came to hand. In addition, the cases of fibrosarcoma of the breast to be found in the files of the Huntington Hospital in Boston were reexamined with regard to the histologic observations and clinical course of the tumor. A grouping was made, separating those tumors in which there was an admixture of epithelial elements such as glands or ducts from those in which the tumor was entirely composed of fibroblasts. Of the total of fifteen cases, seven cases including the two personally seen were found to present features which justified the first diagnosis, namely, "adenofibrosarcoma."

Comparison with other statistics is not justified because of the small number of cases here reported, but in general it may be noted that Ewing states that true adenosarcoma of the breast is rare, while Deaver and MacFarland give a total of 193 cases of adenosarcoma in a group of 838 sarcomas of the breast. S. W. Gross compiled a series of 156 cases of sarcomas of which 33 per cent were termed "adenoid." The most recent compilation is that of Finsterer. Here the terminology must be interpreted, but of forty cases the eighteen which he called "cystosarcoma" might be considered of the type with which the present study is concerned.

Illustrations are appended to demonstrate the activity that is readily apparent in the tumors classified as "adenofibrosarcoma." Mitotic figures are numerous. The cells are frequently anaplastic and the tumor capsules show invasion in many sections. The clinical course in the two groups was compared. Of seven cases in which the diagnosis was "adenofibrosarcoma," five were free from disease when the last reports were received, after periods ranging from six months to seven years. One case had a recurrence four and one-half years after the first operation. The recurrent tumor was histologically "pure fibrosarcoma." The last case showed only a trace of epithelial structure when first seen. Rapid fibroblastic proliferation and two recurrences took place, and death occurred a year after operation. In the second group in which the diagnosis was "fibrosarcoma," the subsequent course remains unknown in four of eight cases. Three of the remaining four patients died with recurrence of metastases within eight months following operation. In the fourth case, which was histologically of low malignancy, the patient was free from disease six years after the operation.

In Finsterer's series the group in which the diagnosis was "cystosarcoma" showed the following clinical course: Of eighteen patients, twelve remained free from disease, one showed recurrence and five died of intercurrent diseases; there were no metastases. Finsterer contrasted these with his group of twenty-one cases of round cell and spindle cell sarcoma, in which only five were free from disease, nine showed recurrences, three showed metastases and the remainder were not followed.

From the present group and that reported by Finsterer one is led to conclude that the prognosis in sarcoma of the breast does not depend entirely on the ordinary criteria of cell activity, but also on the type of tumor, especially with regard to the presence of epithelial elements. In those cases in which epithelial lined clefts are found, metastasis is apparently rare, and there is a good chance for cure by local removal. In no case in either Finsterer's series or ours were there metastases to the regional lymph nodes either primarily or after operation, so that it seems unnecessary to perform a radical operation. I also feel that grouping cases in this way gives one an insight as to the biologic history of these tumors, in that the gradation from simple adenofibroma to more and more malignant sarcomas may be traced, adenofibrosarcoma being an intermediary form which may later or on recurrence become converted into the most malignant form, the pure fibrosarcoma.

DISCUSSION

NICHOLAS ALTER: I think that the cancer campaign and modern surgery have helped us to reconstruct the stages of certain pathologic lesions like sarcoma of the breast, and to explain its histogenesis. We used to talk generally about spindle cell sarcoma of the breast. It was striking to me for a long time that many of the so-called sarcomas of the breast were well encapsulated. Now we get many of these tumors in the earlier stages. I had an opportunity not long ago to study a few cases in which the epithelial structures were very clear, and it is not impossible that all spindle cell sarcomas of the breast come from the innocent-looking intracanalicular fibro-adenoma. This remains encapsulated even when undergoing the more advanced stages of malignant transformation, until the sarcoma becomes extensive and the capsule is lost by the diffuse invasion of the surrounding tissues. In this case the epithelial structures may be quite obscure. These extensive sarcomas are now rare because the patients are operated on much sooner, and fortunately we see more of the early stages of the sarcomatous changes of the intracanalicular adenofibroma.

LAWRENCE SOPHIAN: I think that these tumors go through a series of changes beginning with adenofibroma, passing through the stage which we recognize as adenofibrosarcoma and then going on to pure fibrosarcoma; this is brought out by two of the cases which I reported, which went through these stages. A feature about these cases which may be important from the clinical point of view is that in no case of Finsterer's or of mine were the lymph glands the site of metastases,

no matter how malignant the tumor appeared, which shows that in these cases, the performance of a radical operation is unnecessary.

HARRISON S. MARTLAND: Have any of these metastasized to the lungs?

LAWRENCE SOPHIAN: Yes.

HARRISON S. MARTLAND: They behave like osteogenic sarcoma, then.

LARGE FIBROSARCOMA (?) IN THE PLEURA. ANGELO M. SALA.

A colored woman, aged 40, was admitted to the Harlem Hospital with symptoms of intermittent pain in the right side of the chest and a sense of fulness of the throat, of three months' duration. A roentgen diagnosis was made of a tumor in the right pleural cavity, compressing the lung. There were no evidences of metastases.

At operation the pleura was found covering a tumor mass, which was hard and about the size of a coconut. The pleura was incised. A plane of cleavage was found between the tumor and the surrounding tissue, and the tumor was easily separated anteriorly and posteriorly, but it was firmly adherent at the diaphragmatic surface.

As the patient's condition suddenly became alarming, the operation was stopped. Death followed in an hour. Inspection and removal of the tumor were allowed, but a complete autopsy was refused.

The tumor was easily enucleated, but it was found adherent to the diaphragmatic surface by a broad pedicle. It weighed 1,765 Gm. and was completely encapsulated. It grossly resembled a huge uterine fibroid.

The histologic picture seemed to be that of a fibrosarcoma. Although there were areas suggestive of endothelioma, the growth as a whole more closely resembled a neurogenic sarcoma. One could question whether the tumor arose from the pleura at all, it being an encapsulated growth, and not diffuse. If it was a fibrosarcoma, its rate of growth must have been exceedingly slow. This type of tumor, as a matter of fact, has been reported as developing for years. We have no way of knowing how long the tumor in question has been growing to attain its size. This type of tumor does not metastasize, and from this standpoint one might well call it a cellular fibroma rather than a fibrosarcoma.

DISCUSSION

HARRISON S. MARTLAND: How did the patient die?

A. M. SALA: Of operative shock.

HARRISON S. MARTLAND: How did death occur in the other cases?

A. M. SALA: From pressure symptoms.

ALFRED PLAUT: Even without having seen the slides to which Dr. Sala has referred, I do not think it is probable that this tumor is an endothelioma. The term "endothelioma" has been used or abused very much, but it is disappearing slowly from the literature. Some of you will remember Dr. Klemperer's demonstration not very long ago, and my demonstration several years ago. The tumors probably originate from the lining cells of serous cavities. These cells have the power to develop epithelial structures on the one hand, and typical connective tissue structures on the other hand. In tissue cultures Maximow has succeeded in getting both forms from the lining cells. They are generally called mesothelioma, or celothelioma, which means the lining cells of a large cavity. Even if this slide should show pictures to indicate a connection between blood vessel cells and tumor cells, that would not induce me to call it an endothelioma when most of the tumors show a homogeneous structure without any arrangement characteristic of true endothelium.

A. M. SALA: If we accept this tumor as a pleural tumor, Dr. Plaut's contention is to the point, but then we might both be speaking of the same thing in different terms. The name mesothelioma is also a generic one, presumably sus-

ceptible of as much use and abuse as endothelioma. The concept of mesothelioma as outlined by Dr. Plaut still has to be accepted by many, and I personally have no definite opinion on the point.

ANEURYSM OF THE BRONCHIAL ARTERY. ANGELO M. SALA.

A colored man, aged 35, was admitted to the hospital in extremis and died in four hours. Autopsy disclosed an aneurysmal sac involving the bronchial and the first two intercostal arteries on the left side, and compressing the esophagus and trachea and the left stem bronchus at its origin. The syphilitic nature of the disease was proved histologically.

DISCUSSION

CHARLES NORRIS: From the pictures shown I believe that it is an aneurysm of the ductus arteriosus.

E. LIBMAN: There seem to be three distinct openings.

ANGELO M. SALA: No ductus was found, and there were three distinct openings in the sac.

ANEURYSM OF AORTA RUPTURING INTO SUPERIOR VENA CAVA. LAWRENCE H. COTTER.

The case is presented because it is a typical one of aneurysm rupturing into the superior vena cava, with all the characteristic signs except pain.

A. R., aged 38, was admitted to Gouverneur Hospital on Aug. 30, 1929. The chief complaints were: (1) cough and dyspnea; (2) swelling and dark discoloration of the face and neck; and (3) dizziness and headache. There was no past history of cardiac disease or syphilis. While boarding a truck, the patient was suddenly seized with a choking sensation and a cough. He felt a throbbing in his head and had a sensation of dizziness. Simultaneously a friend called his attention to the fact that his head, neck and hands were blue. He also had headache, but at no time had pain in the chest. These symptoms were present when the patient was admitted to the hospital two hours later.

On physical examination, the patient appeared acutely ill; he lay in bed in an orthopnoeic position, with marked respiratory distress. The head, neck, arms, hands and upper half of the trunk were swollen and cyanotic. The lower margin of the edema and cyanosis was about 2 cm. below the nipples, and the margin was rather sharp. Examination of the eyes showed the conjunctivae to be edematous and engorged; the retina showed marked engorgement of the veins and numerous small hemorrhages. The mucous membranes of the mouth were cyanotic. The heart showed apex impulse in the seventh interspace, anterior axillary line. There was dulness over the upper sternum and to the right and left. There was a loud systolic and a blowing diastolic murmur heard at the base of the heart and along the left sternal border. The pulses were Corrigan in type. The blood pressure in the right arm was 190 systolic and 0 diastolic, and in the left arm 175 systolic and 20 diastolic. The edge of the liver was 5 cm. below the costal margin. The Wassermann reaction of the blood was +++. The red blood cells numbered 3,700,000 and the white blood cells 17,000. The nonprotein nitrogen was 128 mg. per hundred cubic centimeters. Roentgen examination showed an aneurysm of the aorta and cardiac hypertrophy. The temperature was 99, the pulse 120 and the respirations 24.

The clinical diagnosis was aortic insufficiency and aneurysm of the aorta with rupture into the superior vena cava. The specimen showed aortitis which involved the aortic valves, the ascending, transverse and descending aorta, with considerable dilatation. There was an old rupture about 3 cm. in diameter which is about 3 cm. above the aortic ring; a false sac had formed, the walls of which were made up of the superior vena cava and the aneurysmal sac. There was a fresh rupture about 1 cm. in diameter into the superior vena cava 5 cm. above the auricle.

It seems that the aneurysm of the aorta must have ruptured to form the false sac at some time previous without giving any symptoms.

DISCUSSION

HARRISON S. MARTLAND: As I recall, Wayne Babcock recently advocated the surgical shunting off of the blood supply of an aneurysm into the veins of the neck. That was almost done here, was it not?

LAWRENCE H. COTTER: Yes, in this case the patient lived for two days.

CASE OF SCHILDER'S ENCEPHALITIS. L. W. SMITH AND I. SCHEFFER (by invitation).

An unusual case of Schilder's disease in a young Jew, aged 24, was presented. The onset of the disease dated back probably eleven years, when he had an attack of grip, followed by pain in the lower part of the back and difficulty with locomotion. The condition subsequently improved. At the age of 20 he had an attack diagnosed as encephalitis, lasting about a month, when he developed muscular weakness with shakiness of the arms and hands. This progressed steadily up to the present illness. The mentality had apparently not been retarded and he had done well in his school work. The present illness began three days before admission, with fibrillary spasm of the muscles on the right side of the face. He had lost speech since this time and had apparently been unconscious at intervals.

On physical examination the patient appeared emaciated, but otherwise fairly well developed. He was having constant jacksonian convulsions, which involved chiefly the left arm and leg. The eyes were staring, with the pupils unequal and nonreactive to light, with a slight horizontal nystagmus. Between the convulsions the face presented a typical parkinsonian mask. There was no rigidity of the neck, but both Kernig's and Babinski's reflexes were positive. There was moderate spasticity of the extremities, with hyperactivity of the deep reflexes. The spinal fluid was clear and under slightly increased pressure, with a normal cell count. The patient became progressively worse, with a temperature of 104.8 F., and died in convulsions.

The pathologic observations proved entirely negative, except for the central nervous system. There was no definite atrophy, but the consistency of the brain in the region of the right motor cortex was diminished. Coronal sections, after fixation, showed the typical gelatinous degeneration of the subcortical white matter in Schilder's disease. This was most marked in the right frontal lobe, extending posteriorly to the parietal region, but disappearing in the occipital lobe. Similar, but less extensive, changes of the frontal lobe were noted on the left side. It was difficult to make out any gross changes in the cerebellar lobes, pons, medulla and spinal cord.

Microscopic examination showed a demyelinization of the subcortical white fibers as originally described by Schilder. This was accompanied by secondary degeneration of the axis cylinders. About the edge of the demyelinated areas, the reaction was most marked, with the broken down myelin taken up as amorphous lipoids by various phagocytic cells, especially the compound granular cells developed from the microglia. The oligodendroglia showed edema and general cytolysis. The microglia showed extensive hyperplasia, many of the cells forming giant cells.

The picture, as a whole, may be summed up as a severe, relatively localized, toxic degenerative process of the brain which ended, theoretically at least, in a diffuse gliosis. In addition to these observations, there was a picture of diffuse perivascular hemorrhage strongly suggesting hemorrhagic encephalitis, such as one sees both in the epidemic form and in influenza.

DISCUSSION

HARRISON S. MARTLAND: Was the hemorrhagic feature in this case a late lesion or did it occur earlier in the disease?

L. W. SMITH: I am inclined to think that there was a hemorrhagic factor earlier in the course of the disease, as evidenced by the tremendous hemosiderin reaction practically everywhere in the sections, whereas the acute hemorrhagic picture was merely terminal.

HARRISON S. MARTLAND: Were the hemorrhages ringlike in character; i. e., were they confined chiefly to the so-called Virchow-Robin space?

L. W. SMITH: Yes, but many of them were much more extensive.

HARRISON S. MARTLAND: It makes me think of the pictures seen in that type of traumatic cerebral hemorrhage characterized by multiple punctate hemorrhages in the deeper portions of the brain, i. e., the so-called concussion hemorrhages. In the late stages of punch drunk we have described lesions somewhat similar, due to a replacement gliosis in the areas of former hemorrhage. We called attention to the difficulty, in the late stages, of distinguishing these traumatic injuries from the lesions seen in paralysis agitans, disseminated sclerosis, progressive lenticular degeneration, chronic epidemic encephalitis, and some of the so-called hemorrhagic forms of influenzal encephalitis.

CHARLES DAVISON: Was there any round cell infiltration, and what was the state of the axis cylinders?

L. W. SMITH: The condition of the axis cylinders roughly corresponded to the original descriptions. Centrally they had disappeared, but in the periphery one still could find vestiges of them. There were places of definite perivascular round cell infiltration.

HARRISON S. MARTLAND: The same picture is also seen in hemorrhagic encephalitis following the administration of arsphenamine. Were these lesions chiefly in the cortex of the brain or in the deeper portions?

L. W. SMITH: They were subcortical; the cortex itself practically escaped. There was a sharp line of demarcation between the actual cortex and these lesions, but they extended down as far as the fourth ventricle and the pons to a limited extent.

During the last seventeen years there have been fifty-three cases of so-called Schilder's disease reported under various names: some as Schilder's disease, some by the anatomic name, encephalitis periaxialis diffusa, the four cases by Globus and Strauss a year or two ago under the term progressive degenerative subcortical encephalopathy, and others by comparable terms. The chief aim was to differentiate between those which are definitely inflammatory or infectious in nature, and those which are of a toxic degenerative character. This case frankly puzzles us as to the group in which it should be catalogued, because clinically it presents the features of an inflammatory disease, while histologically the picture is almost entirely that of a degenerative one, except for this acute hemorrhagic process, so that I do not know whether Schilder's disease is an absolute clinical or even a pathologic entity. Most of the cases have been reported in comparatively young persons. The duration has been from four days to eleven years. One man, aged 65, who had had a history of progressive cerebral lesions over a considerable number of years, presented evidence of diffuse sclerosis of the brain. The relationship of the cerebral lesions to the cord lesions, multiple sclerosis and lateral sclerosis, is however extremely problematical, and I do not feel that any of us at the present time are in a position where we can make a definite statement as to the absolute entity of this condition, but it does present certain anatomic features which are relatively constant.

ANOMALOUS RAMIFICATIONS OF THE CORONARY ARTERIES. WILLIAM ANTOPOL AND M. A. KUGEL.

Three hearts were shown in which the left anterior descending coronary artery arose independently from the left anterior sinus of Valsalva. The artery lying in the bed of the left circumflex coronary artery apparently arose from an independent opening in the right anterior sinus of Valsalva, immediately posterior to

the mouth of the right coronary artery. This vessel first pursued a course similar to that of the anastomotic artery type II of Kugel, and then continued at the left border of the heart as the left circumflex coronary artery.

Reasons are given which make it seem probable that this anomalous origin of the left circumflex artery is due to a developmental absence of the first portion of the left circumflex coronary artery, with a resultant widening of anastomotic artery type II which takes over its function.

One of the cases showed atherosclerotic narrowings and closures of the right coronary artery and the left anterior descending coronary artery. The nutrition of the heart was good for some time, however, because of the patency of the first portion of the left anterior descending coronary artery and the entire anomalous vessel.

DISCUSSION

M. A. KUGEL: There are two other factors which may play a part in maintaining the circulation in the heart with multiple closures of the coronary arteries: First, according to Wearn, the thebesian system can take over the circulation when the mouths of the coronary arteries are gradually closed. He has reported two interesting cases in which there was complete closure of the mouths of both coronary arteries due to syphilis of the aorta in these regions. Apparently, in these instances the nutrition of the heart was maintained by the thebesian system.

Secondly, we found that some of the occluded vessels were recanalized and this also probably aided in maintaining the coronary blood flow.

There are many cases reported in the literature of single coronary arteries, one of which was described by Dr. Plaut.

It is conceivable that the absence of one coronary artery either due to congenital or postnatal closure of the other coronary artery may become clinically significant in that sudden closure of the remaining coronary artery (at its mouth) would probably result in immediate death. In our cases, in which there was an accessory coronary artery, one can imagine that in the event of closure of one or even two coronary arteries, the accessory vessel through its anastomoses would be able to maintain the coronary circulation if the person survived his attack of thrombosis of the coronary arteries.

EMANUEL LIBMAN: In regard to the canalizing vessels, we used to think of them as important in case of coronary thrombosis, but Dr. Baehr several years ago found that the canalized vessels were apt to undergo sclerosis again, and that they did not play as large a rôle in the nourishment of the heart as was believed.

When it comes to the question of death in these cases, there are several questions involved: the suddenness and the completeness of the closure, the size of the vessel involved, the suddenness of the atherosclerosis in the other arteries of the heart, and the presence of such vessels as have been described here.

LOUIS GROSS: I should like to point out one or two anatomic facts in connection with this vessel, which may be of some interest. You will recall that the right coronary artery arises from this point of the aorta (illustrated) and that from it in turn there arises the anastomotic artery type II which Dr. Kugel described in detail. In the anomalies that were shown, the anastomotic vessel arose from the sinus of Valsalva instead of from the main vessel. It must be realized, however, that there are all sorts of variations as to the site of origin of a branch. It can arise directly from a main coronary vessel or it may arise independently from the aorta. I bring out this point in order to show that if the vessel arises from the sinus of Valsalva and not from the main vessel, it does not necessarily militate against its acceptance as a branch from the right coronary artery.

There is another interesting point with regard to these three cases to which I should like to call your attention. It may be a matter of speculation, but we have here some suggestion of an experiment that nature has made for us. The two normal hearts which Dr. Antopol presented showing this anomalous vessel were in patients aged 64 and 67 years respectively. The left descending vessel in both these cases was remarkably free from arteriosclerosis, even at the site of

predilection for this condition. In the third case there was arteriosclerosis of the right coronary artery. It is obvious that an independent origin of the left coronary artery shunts much of the blood away from the opening of the anterior descendens. The question that arises is whether this fact is responsible for the absence of arteriosclerosis at this customary site in the left descendens. I suggest this as it seems interesting that all three cases should lack the lesion so frequently found.

ALFRED PLAUT: I should like to continue in the direction in which Dr. Libman has begun. Are we going to be able by continued study of coronary anastomoses to explain the fact that one patient dies suddenly and another patient dies more slowly, and still another survives his coronary lesion for a long time? I am rather skeptical about it. Autopsy revealed a heart with narrowing of the coronary arteries; the wall of the artery was entirely stiff, certainly unable to be closed by spasm. Nevertheless this patient had a sudden attack of angina pectoris and suddenly died. There is a report by Oestreich in which autopsy disclosed a complete old thrombosis of one coronary artery and an obturating embolus in the other coronary artery. We should have expected this man to drop dead. He did not. He lived half an hour after his first sign of cardiac distress. Chiari reported a similar case with death fifteen minutes after the beginning of the attack. Many years ago, Krehl spoke about the X-factor which is interposed between coronary lesion and sudden death. We certainly do not always see a correlation between the extent of the coronary lesion and the suddenness of death. Dr. Kugel just said, that a good many cases of absence of one coronary artery are reported in the literature. There are a good number of cases described under this heading, but I do not think there is any one in which there is really absence of the artery. When I published my paper nine years ago, I was careful to simply label it "Blood supply of heart from a single coronary artery." The right coronary artery in our specimen seemed to be missing, but I found a small round dot in the sinus of Valsalva which probably was a rudiment of the artery. Most of the other cases reported are nothing but anastomotic branches from the other coronary artery. Eighty years ago this was plainly stated by Hyrtl.

The comparative anatomy of the coronary arteries is interesting: two coronary arteries develop, with separation of the heart chambers; in fishes and amphibia there is only one coronary artery, and in *Chelonidae* and *Sauridae* there is some variation in the number. For nearly a hundred years Kamper's alleged statement that the elephant has only one coronary artery has been quoted. I had an opportunity of seeing the heart of an elephant, and there were two coronary arteries. I went back to Kamper's original description of the elephant's heart. It simply stated that the heart had only one coronary artery, but this divided into two branches directly after the origin of the aorta.

HARRISON S. MARTLAND: In syphilitic aortitis in which there has been a slow atresia or stenosis of the orifices of the coronary arteries, what in your experience has been the condition of the heart muscle? Do you not often find just a nutritive disturbance without extensive scarring?

WILLIAM A. ANTOPOL: We have one case similar to that with almost complete occlusion at the mouth of the right coronary artery. In this case there was dilatation of the anastomotica type II, which joined the left with the right circumflex. It seems as though the right side of the heart was supplied by blood from the left coronary artery by means of the anastomotica. There was no extensive scarring.

HARRISON S. MARTLAND: It would seem that these anomalies must be fairly common. Clinically they are of great importance in the establishment of compensatory circulation in occlusion or atresia of the coronary arteries. Unfortunately it is quite impossible for most of us to study these hearts properly on account of the great amount of time and the difficult technic required.

WILLIAM A. ANTOPOL: The time factor is important. If there is a sudden occlusion and there is no time for anastomosis to develop, it is quite obvious that

there will be no dilatation, but if it is a slow process, like syphilitic aortitis, communicating channels will develop.

CHARLES NORRIS: I have seen a great many hearts, but never one with a single coronary artery. I think the report that only one coronary artery exists is due to careless observation. The observers have probably overlooked the fact that there has been a closure of the orifice, and that sometimes one must look very carefully. I have seen a number of cases in which there was apparently but one orifice, but dissection always revealed the coronary artery, which was of normal width, 10 or 11 mm. in circumference; the circulation had reestablished itself in the coronary the orifice of which was closed. I think it a false observation that anyone has seen in the human heart only one coronary artery.

ALFRED PLAUT: I think I can defend myself by showing Dr. Norris a drawing that I brought, by which we can prove that the one existing artery is sending branches to the whole heart; then I think Dr. Norris's objection will be withdrawn. This coronary artery goes around the whole heart and nearly reaches the point where the other coronary artery should arise. It means that the whole heart belongs to the system of this one coronary artery. If there had been another coronary artery, one could not explain this system which goes around the whole heart. It fulfils the condition which Hyrtl imposed eighty years ago for the claim that a heart has one coronary artery.

LOUIS GROSS: This should not necessarily fulfil all the conditions. In this diagram, if this left anterior descendens arose further along the course of the left circumflex and it may very well do so, and if the circumflex orifice were obliterated, for instance through syphilis, so that all the blood to the left hemicircle came through the anastomotic vessel, much as it is going to the left circumflex in the cases presented here, there would seemingly be a single coronary artery supplying the whole heart. The little brown dots referred to by Dr. Plaut are interesting; in one case we found tiny dots which indicated that the original site of the blood supply from the left side had come from the left anterior sinus of Valsalva. I agree with Dr. Norris that the blood supply originating from a single coronary artery must be a rare condition.

ALFRED PLAUT: In the case I showed, only one vessel comes out from the sinus of Valsalva. There is no branching near the origin. Here (lantern slide demonstration) is the posterior view of one coronary artery going around the whole heart. We see it emerge from one edge and disappear on the other; these are branches coming out, and probably there is an anastomosis which I could not prove by dissection with scissors and forceps. Here is the anterior picture. This is the left coronary artery, which disappears on the left edge and goes around, and then reappears on the right edge. This is the ramus descendens which goes down to the apex of the heart. But the branch which it gives off to the right is wider than the one which goes down to the apex. In a picture which Henle gives in his "Textbook of Anatomy," he also makes this branch wider.

Why do we know so little, practically nothing, about the embryology of the coronary artery? I remember that ten years ago I could not find anything on its origin. Why is it that with the extensive literature on the malformations of the heart so little is known about the malformations of the coronary artery? Rokitansky hardly mentions them in his monograph.

EMANUEL LIBMAN: I should like to draw attention first to the fact that it is a good thing to look at the pulmonary arteries when studying the coronary arteries, because from time to time an important branch comes from one of the two pulmonary arteries. In the second place, there is a little historical interest to this question of the stenoses of the origin of the arteries. Many years ago I spoke to Sir Humphrey Rolleston about this subject, and he drew my attention to an interesting book by Dickinson in which one of the papers dealt with narrowing of the orifices of the coronary arteries. He described three cases, and among them was the one of Thomas Arnold, Master of Rugby, in whose heart there was supposed to be but one coronary artery. Dickinson took that heart out and

he found there was a second artery with closed orifice. It would be interesting to take a series of hearts in which there is a closure from syphilis and find out how often this type of closure is present, and how often such a vessel as that described by Dr. Antopol and Dr. Kugel is dilated.

The whole subject of the pathogenesis in the clinical picture has never been properly studied, because each man has his own theory. I shall attempt to point out in the next few months that practically every theory that has been suggested in the pathogenesis of angina pectoris is correct, except one, and that is the theory that it is spasm of the heart muscle itself. These theories, however, hold for different cases, and sometimes two theories hold for one case. Therefore it is not possible to talk about death in coronary disease on just one basis. As regards spasm, Dr. Plaut mentioned cases in which spasm is presumed to occur and in which there is disease of the coronary arteries. From the clinical standpoint it is easy to presuppose this. That spasm can play an important rôle in so-called angina pectoris is shown by the fact that there are cases on record of patients with Raynaud's disease who died with angina pectoris and with no lesions whatever. I use the term so-called angina pectoris to cover all the types which we see; I refer to the whole group when I say "so-called." There is one case on record in which the patient had Raynaud's disease of the feet and also of the hands for a long time. The patient developed temporary amaurosis, and the vessels in the eyegrounds were found to be narrowed. That patient had a violent attack of angina pectoris and died; there was no disease of the vessels. I think that if spasm itself can cause death, and that if spasm can cause angina pectoris, we have the clinical evidence to show that it may play a rôle even in cases in which the vessels are diseased. We have the same problem in Raynaud's disease. Everybody who has worked on the problem of thrombo-angiitis obliterans has drawn attention to the symptoms which may occur from spasm. While I think it is difficult to conceive that spasm may occur in these vessels, I think the question should be left open. In the studies which I have made on the hyposensitive state, I have found that general weakness can take the place of local pain in a given disease in which the main symptom is usually local pain. It is possible for a patient at the onset of spondylitis to drop on the floor in shock, and then get up and begin walking. We must begin to study these cases from the standpoint of the hyposensitive condition. I believe that it is possible, especially in a fatal case, for the patient to go into fatal shock. I want to indicate how difficult it is at the present time to discuss clearly all the possible causes of death.

M. A. KUGEL: We presented these vessels only to demonstrate their embryologic, anatomic and possible clinical significance.

CHICAGO PATHOLOGICAL SOCIETY

Regular Meeting, Jan. 13, 1930

HENRY C. SWEANY, *President, in the Chair*

THYROTOXICOSIS PERSISTING AFTER THYROIDECTOMY. DALLAS B. PHEMISTER and P. ARTHUR DELANEY.

L. B., an unmarried woman, aged 41, was seen by Dr. D. P. Abbott in February, 1925, because of nervousness, weakness and palpitation of the heart. She had a fine tremor and tachycardia; there was no exophthalmos, and the thyroid gland was not palpably enlarged. On February 27, the basal metabolic rate was + 12. Rest in bed and the use of compound solution of iodine for two months made no improvement. On July 22, her basal metabolic rate was + 89. Rest and the use of compound solution of iodine again had no effect. On August 20, the basal rate was + 60, and two days later both upper poles of the thyroid were ligated. She did not improve appreciably from the operation, and the

weakness, tachycardia and nervousness persisted. On Jan. 13, 1926, a subtotal thyroidectomy was performed. The thyroid gland was found about normal in size and a small amount of the posterior portion of each lower pole was left behind. The patient improved but slightly after the operation, and two months later she was extremely toxic. On April 20, the basal metabolic rate was + 83. The use of compound solution of iodine for several weeks caused no improvement. At this time a thorough examination was made for accessory thyroid tissue and none was found. The patient then received roentgen therapy from May to October, over the neck and mediastinum. There was no improvement in her condition, and during the autumn of 1926 she was confined to bed for two months with symptoms and signs of cardiac incompetency; there was marked edema of the feet and legs, tachycardia and dyspnea. In January and February, 1927, she was again given iodine and on April 20, her basal metabolic rate was + 41, but she was still confined to bed with signs of cardiac incompetency. In the belief that too much thyroid tissue had been left behind at the first operation, the neck was explored on June 6. An examination was made from the level of the thyroid cartilage to the thoracic aperture and no tissue like thyroid gland was found. There were two small fibrous nodules in the region of the posterior portion of the lower poles. In an endeavor to do something the remnants of the inferior thyroid artery on either side were ligated. Following this operation the patient improved materially for a short time and on June 14, the basal metabolic rate was + 5. Two months after this last operation, however, she was again markedly thyrotoxic and remained so from that time until death. On November 5, the basal metabolic rate was + 57, and on Feb. 8, 1928, it was + 78. She was confined to bed from time to time during the spring and summer of 1928. From June 16 to August 27, the patient received 10 minims (0.6 cc.) of compound solution of iodine three times a day. She did not improve and had a basal rate of + 78. She entered the Billings Hospital on November 6, with a basal metabolic rate of + 85. There had been no appreciable change in her condition. She received extract of suprarenal cortex for two months without effect. On Jan. 10, 1929, her basal metabolism was + 69, and she had marked weakness and signs of a moderate cardiac decompensation. While she was under observation, several blood calcium determinations were made that gave normal results. Information secured from her parents added that about the middle of January, she had a severe attack of acute pain in the region of the right kidney accompanied by chills, a temperature of 103 F. and bloody urine. Early in February, a urinalysis was done that was reported: albumin 2+, leukocytes 1 + and erythrocytes 3 +; on the same date, her leukocyte count was 18,000, erythrocytes 2,800,000 and hemoglobin 50 per cent, while the differential count revealed 90 per cent neutrophils. It is interesting to note that previous to this acute attack the leukocyte counts had been under 10,000, and in the differential examination there was an increase in the lymphocytes up to 62 per cent. The patient died on February 16.

On February 17, autopsy was performed and disclosed, among observations of lesser interest, a slight acute vegetative, mitral endocarditis, hemorrhagic glomerulonephritis and anemic infarcts in the right kidney and spleen. The thymus gland weighed 6 Gm. From the neck, tissues, including and below the thyrocricoid cartilage, were removed and carefully searched for thyroid tissue. Many microscopic sections failed to disclose a solitary thyroid follicle. Material that grossly suggested thyroid tissue, microscopically proved to be a lymph node.

In view of these results following such a persistent thyrotoxicosis, interest was stimulated in making a special histologic study of the thyroid removed as a subtotal resection in January, 1926. Sections were prepared from different levels of four pieces of tissue secured from the Bevan Laboratory of the Presbyterian Hospital, Chicago. The use of a number of different staining methods has enabled us to demonstrate the following conditions: The presence of characteristic lymphoid follicles with germinal centers, with associated lymphoid tissue frequently arranged in the cortex and medulla, and thyroid alveoli free among

the lymphoid tissues; extensive arteriosclerosis with calcification of the thyroid arteries, and of their branches; extensive fibrosis and masses of granulation tissue; two distinctly different types of thyroid alveoli, morphologically and cytologically; (*a*) alveoli of moderate size lined by low cuboidal cells with relatively clear cytoplasm and an average content of vesicular colloid in the lumen; (*b*) smaller alveoli resembling those of compound, serous, alveolar glands, with very small lumen that are often empty, or else contain very little colloid, and lining cells that are tall cuboidal to columnar with a generous quantity of deeply staining granules of mitochondrial type, occasionally seen as isolated or grouped units in the wall of the alveoli described under (*a*).

DISCUSSION

EMIL RIES: Were the ovaries examined?

EDWIN F. HIRSCH: How do the authors explain their results?

GEORGE M. CURTIS: The case which Dr. Delaney has presented raises a number of interesting questions regarding the problem of goiter. It seems open to question in this case whether a complete removal of the thyroid was done. The main portion of the thyroid gland originates at the base of the embryonic tongue in the region of the foramen cecum. This anlage may not descend into the neck. In case it does not, it persists as a lingual thyroid and this may become goitrous. More than 100 cases of lingual goiter have been reported in the literature. At least one of these (Strauss: Med. Klin. **2**:1259, 1906) was associated with mild symptoms of thyrotoxicosis.

The collections of lymphocytes within the thyroid gland, and particularly their organization into a definite lymph nodule, as has been shown, recalls that patients with thyrotoxicosis have, as a rule, lymphocytosis. This may be as high as 65 per cent. A lymphocytosis, however, is not pathognomonic of thyrotoxicosis since it also occurs in endemic cretins. Just what its significance is in thyroid disease is by no means clear.

Calcification of the thyroid arteries in goiter has been well recognized, particularly by Langhans and his school. Jores (Beitr. z. path. Anat. u. z. allg. Path. **21**:211, 1897) demonstrated early changes in the walls of goitrous thyroid arteries leading to arteriosclerosis. These consist of widening of the intima, fragmentation of the internal elastic membrane and finely granular calcification in and about the fragments. Hesselberg (Frankfurt. Ztschr. f. Path. **5**:322, 1910) observed sclerotic plaques in the thyroid arteries of the new-born infant. Isenschmid (Frankfurt. Ztschr. f. Path. **5**:205, 1910) reported arteriosclerosis in the thyroid arteries of infants. Arterial changes may occur early in the walls of the thyroid arteries without a generalized arteriosclerosis, and particularly in endemic goiters. The reasons for these early degenerative changes are not clear.

FRANK SMITHIES: In a given individual or group the amount of thyroid tissue necessary to cause thyrotoxicosis is not known and possibly only a small amount suffices. In a thyroid constitution only a small quantity of thyroid tissue may be necessary to continue the symptoms.

P. A. DELANEY: The ovarian tissues were examined without demonstrating important changes. Dr. Phemister and I are at a loss to explain our results.

THE EFFECT ON MOTILITY OF IRRIGATING A LOOP OF ILEUM OF MACACUS RHESUS MONKEYS WITH SALMONELLA ENTERITIDES AND ITS PRODUCTS. G. M. DACK and R. MERCHANT.

In previous work we had observed that not all monkeys were susceptible to "food poisoning." In the monkeys that were susceptible, however, diarrhea could be produced time after time by subsequent feedings of living *Salmonella* organisms. In the present series, therefore, only such monkeys were used as were known to be susceptible.

Fistulas were made on the ileum of four monkeys, three of the Thiry type and one of the Thiry-Vella type. Motility of the loops was studied by the balloon method.

Irrigation of the loop with heat-killed cultures and filtrates of *S. enteritidis* (550) did not produce any striking changes in motility and tonus.

Observations were made on the stools of one monkey with a Thiry fistula and one with a Thiry-Vella fistula. No diarrhea followed the irrigation of the loops with heat-killed cultures, filtrates or living suspensions of *S. enteritidis*. Living organisms, however, when fed produced a diarrhea in the monkey with the Thiry-Vella fistula, without affecting the loop motility.

Endoplates streaked with the loop contents of the monkey with the Thiry-Vella fistula showed few or no colonies. No *S. enteritidis* organisms were recovered from the loop thirty hours after irrigation with a living suspension of *S. enteritidis*.

INTERMITTENT FECAL ELIMINATION OF BACTERIA IN CHRONIC BILIARY CARRIERS. LLOYD ARNOLD and A. J. NEDZEL.

There are certain demonstrable changes that take place within the gastrointestinal tract during the process of adaptation to external stimuli, such as alterations in climate and in diet. The bacterial content of the lumen of the upper half of the small intestine is low and consists of enterococci in normal animals, including man. This bacterial flora is not changed by the ingestion of bacteria. These exogenous strains are destroyed within this part of the intestinal tract. The simple and scanty bacterial life within the lumen of the duodenum and jejunum is a constant observation for normal animals.

The bacterial contents of the small intestine can be changed in several ways. We have found that a warm temperature environment will cause a change in the bacteria in the duodenum and jejunum. Accompanying this change in the endogenous bacterial flora there is a loss of the power to destroy ingested bacteria. When bacteria are injected directly into the duodenum of normal animals few of them can be found in the cecum. When the same experiment is performed in a warm temperature room, many of them reach the cecum and remain viable for hours. This shows that the intestinal tract can destroy bacteria independent of the stomach.

B. prodigiosus was injected into the gallbladder of dogs under sterile precautions. Nonleaking appendiceal fistulae were established. After from seven to ten days six animals showed no *B. prodigiosus* in the cecal contents; four animals had a few isolated colonies after direct plating of the contents. When these animals were placed in a warm and humid room for three hours, many *B. prodigiosus* were present in the cecum and persisted for many hours. Agar stab cultures of *B. prodigiosus* were sewed into the lumen of the gallbladder in dogs. This led to a more persistent carrier state and more of these microorganisms could be found in the cecum from one to four weeks after recovery. When these animals were placed in the hot room, many more bacteria appeared than in ordinary temperature rooms. This was a substantiation of our previous experimental work, namely, that interference with the self-disinfecting power of the small intestine would allow patients who have recovered from typhoid fever some time ago to become fecal carriers. The hot weather causes an interference with the bacterial killing power of this region of the intestinal tract. Patients recovered from typhoid fever who show an absence of *B. typhosus* in the feces may have small lesions along the biliary tract that eliminate these bacteria into the duodenum, but under normal conditions they are destroyed before reaching the large intestine. If the self-disinfecting power of the small intestine is absent, then such persons would be carriers. The same is true of the water-borne and food-poisoning diarrheas.

In many instances the epidemiology of typhoid fever following a water-borne diarrhea or food-poisoning epidemic has been difficult to explain. No bacteria

resembling the typhoid group can be isolated from water or food in a great many instances. The appearance of typhoid fever in the warm months of the year has been difficult to explain epidemiologically. The ingestion of polluted water causes diarrhea. There is a loss of the self-disinfecting power of the upper part of the small intestine during diarrhea. The same is true of diarrhea due to food poisoning.

DISCUSSION

FRANK SMITHIES: Were the results with tissue-invading organisms such as *B. typhosus* the same as with the lumen-dwelling organisms?

L. L. ARNOLD: We could not work quantitatively with organisms of the typhoid group as well as with the nonpathogenic chromogens used.

BIFID APEX OF THE HEART OF A GUINEA-PIG. H. B. HANSON.

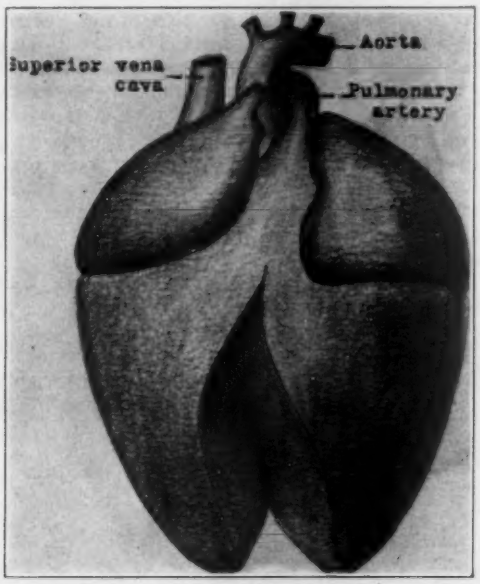
A more or less complete congenital separation of the ventricles of the heart through the septum is known as bifid apex of the heart. Judged by the dearth of recorded accounts it seems to be a rare anomaly. I have found only four references to this anomaly in human hearts published in ninety years. H. D. Rolleston (Bifid Apex of the Heart, Tr. Path. Soc. London **43**:37, 1891-1892) described briefly the heart of a woman, aged 40, who died of stenosis of the mitral and aortic valves. The apex of the heart was formed by the left ventricle, and extending from the right side of this was a second apex, that of the right ventricle. A. W. Meyer (Hearts with Bifid Apices, Anat. Rec. **9**:524, 1915) published illustrations of two hearts with deeply notched apexes but included no descriptive details. F. P. Mall (Bifid Apex of the Human Heart, Anat. Rec. **6**:167, 1912) recorded a heart with bifid apex found in a cadaver at Johns Hopkins University. The cleft was 2 cm. deep, and the anomaly was attributed to an arrested development of the apex in an embryo more than 11 mm. long. Maude E. Abbott (Congenital Cardiac Disease in Osler, William: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1928) stated that in her list of 850 congenital cardiac defects, bifid apex occurred fifteen times with and independently of other defects. She also referred to Theremin's 106 cases in which bifid apex occurred three times.

According to F. P. Mall (On the Muscular Architecture of the Ventricles of the Human Heart, Am. J. Anat. **11**:211, 1911), the superficial muscle fibers of the ventricles are divided into two main groups. One system, the "bulbospiral" band, arises from the conus arteriosus and the root of the aorta. The other, the "sinospiral" band, has its origin from the region of the primitive venous sinus. The fibers of each of these systems normally cover portions of each ventricle. They extend from above obliquely downward and at the apex all are coiled into a whorl or vortex. From this all pass to the interior of the walls and then back to the base of the ventricles, some in the septum and others in the papillary muscles. Mall stated that a bifid apex results when there is a defect in the formation of the normal muscular vortex. This occurs because the sinospiral muscle band does not reach the apex of the left ventricle, and the apex, therefore, is formed by the bulbospiral band and consequently the interventricular groove persists.

According to Mall, bifid apex is commonly found in some marine animals such as the dugong, but no reference could be found of its occurrence in any of the higher vertebrates although texts on comparative anatomy, embryology and various species of animals were examined. Dr. W. J. Osgood, curator for the department of zoology at the Field Museum, Chicago, assisted in offering his library and that of the museum for additional study, but here also no information was found regarding bifid apex of the heart in the higher vertebrate forms. It is impossible to estimate, therefore, the frequency of occurrence of this anomaly in the higher vertebrates.

During the routine postmortem examination of a guinea-pig in the laboratory of St. Luke's Hospital by Miss Marian Barnes, the ventricles of the heart were found to be separated along the interventricular septum. Since an average of 250 guinea-pigs is examined postmortem each year in this laboratory without an anomaly of this kind having been noted, this congenital deformity was considered to be rare. A careful examination of the heart was then made and a search established for reports of a similar anomaly in man and the higher animals.

The heart with its thin, transparent pericardium occupied the usual position in the thorax. After the pericardium had been opened there was a median longitudinal division of the septum and although the ventricles were close together they were separate and each had a complete wall of its own. The septal surfaces of the approximated ventricles were smooth and glistening and had no hemorrhages such as occur in freshly divided tissues and which would have been present had the septum of the heart been accidentally divided by the scissors



Ventral view of the heart, illustrating the extent of bifurcation of the apex.

used in opening the pericardial sac. The approximated surfaces did not lie in a straight sagittal plane, but instead the septal wall of the right ventricle was a concave surface that cupped itself over the convex septal surface of the left ventricle like the approximated paired kernels of a double almond. The heart was then removed with the stumps of the large vessels intact. The anterior length of the left side of the heart from the root of the aorta to the apex was 2 cm. and the right, 1.9 cm. The fissure mentioned extended on the anterior surface from the apex upward 1.2 cm. to the lower margin of the left auricular appendage and on the posterior surface upward 0.7 cm. The apex was thus completely divided for a length of 7 mm. The dorsoventral diameter of the heart at the upper level of the fissure ventrally was 1.1 cm. and the dorsoventral extent of the fissure at the same level was 1 cm. The remainder of the ventricles above the completely divided apex were therefore connected only by a band of myocardium about 1 mm. in thickness on the posterior surface of the heart. There was no connection below between the ventricles. The large vessels at the base of the heart had the usual relations. The ductus Botalli was closed but a fibrous cord persisted 0.4 cm. long and 0.1 cm. in diameter.

The inside length of the left ventricle from the mitral ring to the apex was 1.1 cm. and from the attachment of the aortic leaflets to the apex it was 1.3 cm. The thickness of the myocardium of the left ventricle measured along the septum behind at the level of the mitral ring was 3 mm. The length of the right ventricle from the tricuspid ring to the apex was 1.1 cm. and from the attachment of the pulmonic leaflets to the apex it was 1.4 cm. The thickness of the myocardium of the right ventricle measured along the septum in front was 1 mm. The diameter of the tricuspid ring was 7 mm., of the pulmonic 2 mm., of the mitral 6 mm. and of the aortic 2 mm. There were no abnormalities of the leaflets of any of the valves.

The heart described in this report was unusual in that the ventricles were separated at the auriculoventricular junction.

Book Reviews

MOLECULAR PHYSICS IN RELATION TO BIOLOGY. Report of the Subcommittee on Molecular Physics, of the National Research Council. Price, $3. Pp. 293, with 71 line-cuts and 2 plates. Washington, D. C.: National Research Council, 1929.

The National Research Council has performed a useful service in publishing this compilation of contributions which serve notice that molecular physics is hereby recognized as one of the official routes for invasion of the problems of biology. As du Noüy says in his stimulating introductory chapter, "Molecular physics deals mainly with the physical properties of molecular arrangements. The name itself is relatively young, but the techniques employed are those of physics, of physical chemistry, and of chemistry, and for that reason, it may be said that most biologic problems depend on molecular physics for their solution. An isolated phenomenon may be of chemical nature, yet its consequences, in the organism as a whole, may be purely physical." Actually, molecular physics covers the same ground more familiarly designated by the term colloidal chemistry, and the theme of this volume is largely a reiteration of the well known fact that biologic phenomena are not all due to reactions between chemical valences, but also to physical interaction between large molecules. Du Noüy stresses as the main objective the enlisting of the interest and cooperation of physicists in the problem of biology by placing before them these problems, not as isolated mysterious units, but as expressions of the same fundamental principles and laws which govern the inanimate world, and to direct their attention to the existence of this bridge, "directly connecting physics and chemistry over the chasm of chemical methods."

The several authors each present brief statements of their own particular fields of interest, starting out with Ascoli's description of his miostagmin reaction which he brought out in 1909 as a new method for investigation of immunologic reactions by observing the change in surface tension accompanying them. He admits that the general neglect of this method by immunologists is justified by its inferiority to other methods as a practical diagnostic procedure, but presents claims as to its possible value in the diagnosis of cancer. This paper seems out of place among the following much more definite articles, which deal mostly with exact and comprehensive observations. Thus, Chambers describes the work that has been done, largely by himself, in estimating the hydrogen ion concentration and the oxidation-reduction potential of cytoplasm by micro injection methods. Donnan reviews in three pages the investigations that have been made on the Donnan equilibrium, and points out that the general thermodynamical equation which is applicable to the case of ionic membrane equilibria has been lying buried all these years in Willard Gibbs' celebrated memoir on heterogeneous equilibrium. More extensively are presented the principles, methods and mathematics for investigation of surface tension by N. E. Dorsey, and the mechanism of filtration through porous membranes by Leonor Michaelis. Osterhout reviews and summarizes his important work in the permeability of cells, and du Noüy does the same for his pioneering attempts at a study of the physical chemistry of immune serums. Northrop presents a brief statement on the nature of viscosity and its measurement, while Seifriz gives a much more detailed report on the viscosity or plasticity of protoplasm as determined by himself and other investigators. Vlés and de Coulon offer a résumé of their attempts to influence the growth of tumors by modifying the iso-electric point of the tissues. Each article is accompanied by a useful bibliography. It will be seen that these papers are a somewhat heterogeneous lot which present a few isolated, often unrelated topics of interest to the general biologist as well as to the "colloid chemist." Presumably the committee that put out this compilation was largely actuated by thoughts of the careers of the little acorns.

THE CHEMICAL ASPECTS OF IMMUNITY. By H. GIDEON WELLS. Second (revised and enlarged) edition. American Chemical Society Monograph Series. Price, $6. Pp. 286. New York: The Chemical Catalog Company, Inc., 1929.

Immune reactions, irrespective of whether the mechanism involved is colloidal or what one may call strictly chemical in nature, are fundamentally chemical reactions and their study therefore properly belongs to the field of biologic chemistry. The first edition of this book, which appeared about four years ago, was, however, the only one, at least in the English language, which emphasized the chemical aspects of immunology. Although the general plan and purpose of the book remain unchanged, a great deal of material has appeared during the last few years which bears on this subject and which has been incorporated into the new edition. Among the outstanding items discussed in the present revision are "the newer contributions on the influence of lipoids and carbohydrates on antigenic activity and specificity, the refining of antibodies to near the vanishing point, the chemical modification of antigens, the increasing study of isolated antigens, the growing recognition of the differences between complex and simple antigens, and the varied if unsuccessful attacks on the problems of specificity." The author presents a vivid picture of the present state of the relationship between immunology and chemistry which should prove a thrilling adventure to the workers in both sciences, and especially in chemistry, who are not familiar with the important bond between them and the benefits to be derived from each.

The science of immunology, originally concerned with disease, has developed so rapidly in the last quarter of a century that we may well consider it as a border science between biologic and colloid chemistry on the one hand and bacteriology and the other medical sciences on the other, in much the same way that physical chemistry is considered a border science between physics and chemistry. The advances in immunology have been almost entirely empiric, as in any new science, but we are gradually approaching the time when immune reactions may be placed on a sound theoretical foundation. For this purpose, however, we must develop workers who are familiar with the fundamental ideas and methods of both parent sciences. Some of the most important and perplexing problems in biochemistry, such as the structure of the protein molecule, are indissolubly bound up with such problems as the chemical nature and specific reactions of antigens, and any advances in one field are bound to be reflected in the other. Relationships of this sort may be cited in great numbers, and it is because the present volume reviews the progress made thus far in this highly important border science and because it emphasizes the contributions which biochemistry and immunology are capable of making to each other that it forms a stimulating addition to both the chemical and the immunologic literature.

THE RIGHT HONOURABLE SIR THOMAS CLIFFORD ALLBUTT, K.C.B., M.A., M.D., F.R.C.P., F.R.S., HON. M.D., D.Sc., D.C.L.,, LL.D., Regius Professor of Physic in the University of Cambridge. A Memoir. By Sir. Humphry Davy Rolleston, G.C.V.O., K.C.B., M.A., Regius Professor of Physic in the University of Cambridge. Cloth. Price, $6. Pp. 314, with 3 illustrations. New York: The Macmillan Company, 1929.

Clifford Allbutt lived for eighty-nine years. His active medical life, which continued until his death in 1925, covered sixty-five years. He made many additions to medical knowledge and technic and he was for many years one of the most influential, widely respected and honored English-speaking physicians. He invented the form of clinical thermometer now in use; he described syphilis of the cerebral arteries in 1868, before Heubner; he exploited the value of the ophthalmoscope in general medicine; he urged the study of pathology on a comparative basis; he advocated the aortic origin of angina pectoris and separated hyperpiesia (essential hypertension) from other forms of increased blood pressure — to mention only some of his achievements. He maintained consistently throughout his long life a wonderful energy and an unceasing work. "Only two things

are essential — to live uprightly and to be wisely industrious." He was a profound student of the history of medicine, a master of literary style and a scholar in the large sense. He was in rare degree versatile, learned, wise and kind, and his influence went far and deep. The life by his successor as regius professor of physic at Cambridge is concise and compact. It traces his multifarious activities succinctly year by year without losing touch with the man himself, and gives a clear and well defined picture of the life of a great personality.

DISEASES TRANSMITTED FROM ANIMALS TO MAN. By THOMAS G. HULL, Chief Bacteriologist, Illinois Department of Public Health, Assistant Professor of Pathology and Bacteriology, University of Illinois College of Medicine. With an Introduction by Veranus A. Moore, Director, New York State Veterinary College, Cornell University. Price, $5.50. Pp. 352, with 29 illustrations and 43 tables. Springfield, Ill.: Charles C. Thomas, 1930.

In the broad field of comparative pathology there is no subdivision of greater concern to human and to veterinary medicine than the one considered in this book, transmissible diseases common to animals and man.

There are five sections. Section one deals with diseases of domestic animals and birds that may be transmitted to man: tuberculosis, anthrax, foot-and-mouth disease, infectious abortion ("Brucellosis" would be a good general term for the animal and human infections caused by the Brucella group), milk sickness, actinomycosis, smallpox and cowpox, glanders, rabies, psittacosis, food poisoning, swine erysipelas and parasitic diseases, including the broad fish tapeworm. In section two, rodent diseases are considered: plague, tularemia, spirochetal jaundice, ratbite fever and Rocky Mountain spotted fever. The third section is devoted to the relation of certain human infections to animals, e. g., epidemic sore throat, diphtheria and scarlet fever, but diseases like malaria, yellow fever, typhus fever and trench fever, which are conveyed from man to man by insects, are not discussed. Section four deals with animals as passive carriers of pathogenic germs, as illustrated in botulism, tetanus and gas gangrene. In the fifth section is a brief review of the part played by each animal in the spread of human diseases.

There is an author as well as a subject index. If a new edition is published, special care should be used to secure the correct spelling of proper names. This will be a good book to consult mainly for bald facts in respect to the epidemiology and prevention of the diseases that fall within its scope. The historical development of the knowledge of these diseases is given rather full and suggestive consideration.